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TUMORS OF THE SPINE

WITH A CONSIDERATION OF EWING'S SARCOMA

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Originally it was intended to present in this study a classification of primary tumors of the spinal column and of tumors metastasizing to the spine or invading it from contiguous structures. However, it soon becomes evident that Ewing's sarcoma of bone in the region of the spinal column presents certain features of special interest. The relation of this condition to tumors of neuroblastic origin has been given detailed consideration.

This study has been limited, for clinical reasons, to tumors affecting bone. With patients who have pain in the back or symptoms of pressure on the spinal cord, or both, the roentgen study is usually the deciding factor in diagnosis before operative procedures are undertaken. While excellent articles dealing with the roentgenologic diagnosis of spinal tumors have appeared, most of these have dealt with a single type of tumor. For this reason a composite picture with special reference to the incidence of spinal tumors and to their pathology is presented, based on a larger series of cases.

The material used is from the records of the surgical pathologic laboratory and from the neurosurgical department of the Johns Hopkins Hospital. Because of the manner in which this material was collected, the incidence of the various tumors has not been determined with absolute exactness, but for practical purposes the percentages found should be significant.

In all, there were 291 tumors in this series. All of them affected bone or were demonstrable roentgenologically. They included metastatic carcinoma, primary tumors of the spinal column (mainly of osseous origin), glial tumors and tumors of the neural sheath of the spinal cord, tumors of generalized distribution (such as multiple myeloma), tumors of the sympathetic nervous system and tumors of teratologic origin. These types of tumor are mentioned in the order of their frequency.

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METASTATIC CARCINOMA

Metastatic carcinoma was by far the most frequent neoplastic lesion of this series. Of 291 spinal tumors, 172 (59.1 per cent) were metastatic carcinomas. Schlesinger [1] and Frazier,[2] the former obtaining his data from autopsies and the latter taking his from operations, pointed out the marked frequency of metastatic lesions of the spine. In adults such lesions must be considered in the differential diagnosis of any tumor affecting the vertebral column. Table 1 lists the sites of origin of the 172 tumors.

Schlesinger in 13,500 autopsies found 59 metastatic carcinomas of the spine and listed their sites of origin (table 2).

These two tables present notable differences. Prostatic carcinoma is probably not as frequent as is indicated by the figures in table 1, since in obtaining these figures all the patients with prostatic cancer in the Brady Urological Institute of the Johns Hopkins Hospital were

TABLE 1.—*Site of Origin of Metastatic Carcinomas of the Spine Observed in the Laboratory of Surgical Pathology*

Site of Origin	Number of Cases
Prostate	86
Breast	60
Undetermined	14
Gastrointestinal tract	5
Kidney	4
Thyroid	1
Lung	1
Nasopharynx	1
Total	172

examined. It will also be noted that cancer of the female genital tract is not listed in table 1. Behney [3] has shown that of 55 carcinomas of the uterine cervix which metastasized, 5 had metastases to the lower lumbar vertebrae. This should make the condition a frequent source of metastasis to the spine. These and other discrepancies in the two tables are explained by the different methods by which the material was collected. Table 2 undoubtedly shows more nearly the correct incidence.

Carcinoma of the breast may be considered the most frequent cause of metastases to the vertebrae. In a series of 100 carcinomas of the breast metastasizing to bone (Geschickter and Copeland [4]) 60 of the

1. Schlesinger, H.: Beiträge zur Klinik der Rückenmarks- und Wirbeltumoren, Jena, G. Fischer, 1898.

2. Frazier, C. H., and Allen, A. R.: Surgery of the Spine and Spinal Cord, New York, D. Appleton and Company, 1918.

3. Behney, C. A.: Advanced Carcinoma of the Cervix, with a Report of One Hundred and Sixty-Six Necropsies, Am. J. Obst. & Gynec. **26**:608, 1933.

4. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, ed. 2, New York, American Journal of Cancer, 1936.

tumors were found to be in the spine. The condition has no predilection for any particular part of the spine and is usually an osteolytic process, though osteosclerosis may be produced. The site of origin is sometimes not easily detected. The tumor may be small and may pass unnoticed, or, as is so often the case, the carcinomatous breast may have been amputated years before. In case 1 an interval of fourteen years elapsed between the amputation of the breast and the appearance of metastasis in the spine.

CASE 1.—A white woman aged 58 had a breast amputated for carcinoma in 1920. In September 1933 she began to complain of pain in the back. Roentgen examination in April 1934 revealed partial destruction of the body and the left transverse process of the fourth lumbar vertebra. The osteolytic process progressed, and in February 1935 treatment by roentgen irradiation was begun. A roentgenogram taken in June 1935 showed osteosclerosis in the region of the fourth lumbar vertebra (fig. 1). The patient died in September, and autopsy revealed

TABLE 2.—*Site of Origin of Metastatic Carcinomas of the Spine in Schlesinger's*[1] *Series*

Site of Origin	Number of Cases	Site of Origin	Number of Cases
Mammary gland	10	Bladder	1
Esophagus	9	Ovary	1
Thyroid	9	Sigmoid flexure	1
Uterus	6	Rectum	1
Bronchus	5	Kidney	1
Stomach	4	Adrenals	1
Prostate	3	Larynx	1
Gallbladder	2	Pancreas	1
Sinus piriformis	2	Origin not given	1
Total			59

metastatic carcinoma, histologically similar to the primary growth, in the fourth lumbar vertebra, the liver and the lung.

Carcinoma of the prostate is more characteristic in its metastasis to bone. In 134 cases it involved the spine in 86 and showed a marked tendency to appear in the sacral and the lumbar vertebrae. It produces a lesion which is predominantly osteosclerotic. In case 2 the patient lived three and one-half years after the recognition of the metastasis.

CASE 2.—An elderly white man complained of symptoms of urinary obstruction present for six months and of lumbago present for two months. Roentgen examination in August 1927 showed osteosclerosis of the body of the second lumbar vertebra (fig. 2). A conservative operation for prostatic cancer was done at this time and was followed by roentgen irradiation of the prostatic area and of the spine. Roentgen examination in November 1930 revealed generalized osteosclerosis of the spine. The patient died early in 1931.

Case 3 demonstrates that the primary focus of the cancer may remain undiscovered until postmortem examination. It was a case of renal carcinoma.

Fig. 1 (case 1).— Metastatic carcinoma of the breast in the fourth lumbar vertebra. The roentgenogram shows osteosclerosis following irradiation. (Case of Dr. Warner Watkins, Phoenix, Ariz.)

Fig. 2 (case 2).—Metastatic lesion of carcinoma of the prostate in the spine. The roentgenogram shows sclerosis of the body of the second lumbar vertebra.

CASE 3.—A white man aged 66 complained of pain in the back as his only symptom. Roentgen examination in February 1925 showed a destructive lesion in the body of the second lumbar vertebra producing partial collapse. A soft tissue mass was also visible to the left of the spine. Death occurred in May, and postmortem examination revealed a carcinoma of the left kidney with metastasis to the second lumbar vertebra and to the ribs. Figure 3 shows the lesion found at autopsy. The uniform collapse of the body, the "accordion effect" described by Fray,[5] is well shown. The intervertebral disk was well preserved. The metastatic lesions of renal carcinoma are usually osteolytic and tend to occur in the dorsolumbar region when the spine is affected.

In the diagnosis of metastatic carcinoma of the spine it must be remembered that in most cases the lesions are multiple. A solitary

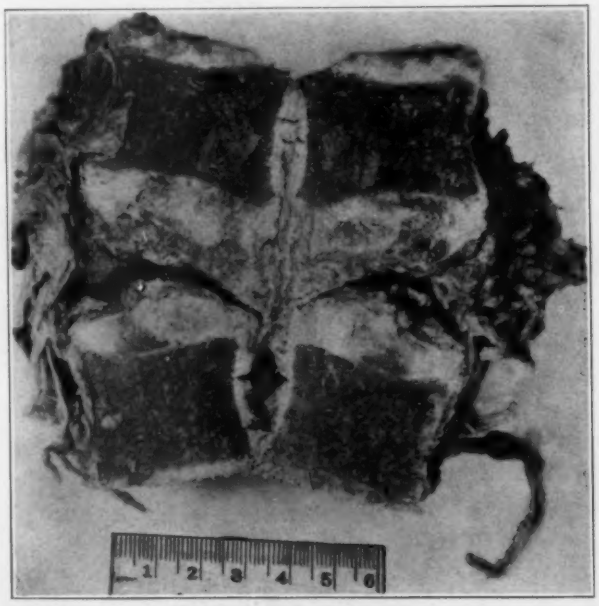

Fig. 3 (case 3).—Hemisection of metastatic renal carcinoma in the spine. The body of the second lumbar vertebra is entirely destroyed. The intervertebral disks are well preserved.

lesion occurred in only 25 per cent of cancers of the breast metastasizing to bone. Consequently, roentgen examination of the entire skeleton is often necessary. A careful search for a primary focus must be made, the most important sites being the breast, the prostate, the cervix, the thyroid, the esophagus and the lung. As may be seen in table 1, a relatively large number of carcinomas of undetermined origin are

5. Fray, W. W.: The Differential Diagnosis Between Infection and Malignancy in Cases of Dorsal Paravertebral Mass, Am. J. Roentgenol. **35**:591, 1936.

encountered. As regards the roentgenologic picture, the tendency of metastatic carcinoma of the prostate to cause osteosclerosis is the only consistently recognizable feature. Roentgen irradiation of the affected area, rest and sometimes operative relief of compression of the spinal cord are indicated. The affected part of the spine should be protected by immobilization or by hyperextension. Life is often greatly prolonged by roentgen therapy, and pain may be controlled.

TUMORS OF GENERALIZED DISTRIBUTION

It is well to consider generalized neoplastic diseases in conjunction with metastatic carcinoma, since multiple myeloma, the most important representative of this group, as regards the spine, is easily confused with metastatic carcinoma.

Among 30 cases of multiple myeloma in the surgical pathologic laboratory there were 14 with leading symptoms involving the spine. Multiple myeloma is a tumor of adult life, the period of its greatest incidence being the sixth decade. The pain in 70 per cent of all cases (Geschickter and Copeland) begins in the lumbar and in the sacral region. In 40 per cent of cases compression of the spinal cord develops. These considerations justify the inclusion of multiple myeloma in a group of tumors affecting the spinal column.

The roentgenogram is often diagnostic. The lesions are rarefied punched-out areas and commonly produce pathologic fracture. They are multiple or become multiple in more than 95 per cent of cases. At times the punched-out areas may be seen in the vertebrae, but more often there is a pathologic fracture (fig. 4). Sacral lesions show the characteristic defects in the roentgenogram.

Because of the age at which its onset occurs and the multiplicity of its lesions, multiple myeloma is difficult to distinguish from metastatic carcinoma. Both, of course, are hopeless conditions, and the differential diagnosis is sometimes of academic interest only. The following points are useful: Metastatic carcinoma is by far the more common. The roentgen picture of multiple myeloma is the more distinctive. The fact that Bence Jones bodies are present in the urine is in favor of a diagnosis of multiple myeloma, and their absence would suggest a diagnosis of metastatic carcinoma, though they may or may not be present with either condition. The presence of chronic nephritis, with nitrogen retention and high serum proteins, is definitely favorable to a diagnosis of multiple myeloma. Biopsy is the last resort. Roentgen therapy is the treatment of choice for both conditions. The lesions of multiple myeloma respond more rapidly than do those of metastatic carcinoma.

Hodgkin's granuloma, lymphosarcoma, myeloid tumors and the xanthomatous lesions were found to be rare or absent in our series of

spinal tumors. Craver and Copeland [6] reported osseous changes in 15.7 per cent of 172 cases of Hodgkin's disease. Vertebral changes are said to be most frequent in cases with skeletal involvement, and these lesions may be either osteolytic or osteosclerosing. Neurologic symptoms are common. High voltage roentgen therapy causes remission of the symptoms, but permanent cure is not established.

There was a single lymphosarcoma in the present series. Craver and Copeland [7] found that bone was involved in 10.4 per cent of 164 cases. They also found that the spine was the most frequent site and that either an osteolytic or an osteosclerotic process may be present. As with Hodgkin's granuloma, compression of the spinal cord may develop. The tumor is radiosensitive.

Fig. 4.—Multiple myeloma of the spine. The twelfth thoracic vertebra is destroyed, and the lumbar spine is displaced laterally. The first lumbar vertebra also shows marked rarefaction.

Various types of myeloid tumors may produce changes in bone. These occur in myeloid and lymphoid leukemia, but so uncommonly that they need only be mentioned here. The osseous changes associated with chloroma are prominent but we found no instance of such involvement of the spine. Porosity and trabeculation of bone occur in erythroblastosis, and in the vertebral bodies these trabeculations tend to be vertical. One such tumor was included in this series.

Hand-Schüller-Christian disease produces circular osseous defects, usually multiple but occasionally single. The skull and the flat bones

6. Craver, L. F., and Copeland, M. M.: Changes in the Bone in Hodgkin's Granuloma, Arch. Surg. **28**:1062 (June) 1934.

7. Craver, L. F., and Copeland, M. M.: Lymphosarcoma in Bone, Arch. Surg. **28**:809 (May) 1934.

are most often affected. When a vertebral body is involved, collapse of that body occurs. We had 1 such case. Anspach [8] reported a case, the patient being a 5 year old boy, in which the body of the tenth thoracic vertebra was involved. Triangular collapse of this body occurred, but with clearcut edges, which distinguished the condition from tuberculosis. With irradiation the lesions of the bone heal in most instances.

BENIGN PRIMARY TUMORS OF THE VERTEBRAL COLUMN

The second largest group of spinal tumors is composed of primary tumors of the vertebral column, which numbered 58 in this series. The relative frequency of the various tumors is listed in table 3.

In all there were 37 benign lesions and 21 malignant lesions affecting the spinal column. Among benign tumors the most common are giant

TABLE 3.—*Primary Tumors of the Vertebral Column*

Types of Tumor	Number of Cases
Benign	
Giant cell tumor	15
Osteochondroma	10
Bone cysts	7
Chondroma	3
Hemangioma	2
Malignant	
Osteogenic sarcoma	
Chondrosarcoma	8
Osteolytic sarcoma	4
Sclerosing sarcoma	4
Chordoma	5
Benign	37
Malignant	21
Total	58

cell tumor (in which type benign bone cysts may be included) and osteochondroma. This corresponds to the relative incidence of these tumors in the rest of the skeleton.

Giant Cell Tumors.—There were 15 giant cell tumors in the present series. In 1935 Murphy [9] collected 45 from the literature and pointed out that the typical history is characterized by injury to the spine in a young adult, followed by pain, tumor and occasionally kyphosis. Symptoms of pressure on the spinal cord may develop. The age incidence in our series is in accord with the findings of Murphy. Most of the patients were young adults. One girl, however, was 7 years of age and one man 62. The incidence of the condition in the male sex exceeded its incidence in the female sex in the proportion of 9 to 5.

8. Anspach, W. E.: Xanthomatosis with Involvement of a Vertebral Body, Am. J. Dis. Child. **48**:346 (Aug.) 1934.

9. Murphy, G. W.: Giant Cell Tumor of the Spine, Am. J. Roentgenol. **34**: 386, 1935.

Eight patients complained only of pain in the back. In 5 instances the pain in the back was followed by compression of the spinal cord. In 1 case the only symptoms were those of pressure on the spinal cord, and in the remaining case the symptoms of this compression preceded the pain in the back. In 6 cases a mass was present. The symptoms and signs depend, of course, on the portion of the vertebra which is involved and on the direction taken by the tumor in its growth.

The roentgenologic picture is variable but often diagnostic. As with tumors of the long bones, the other lesions with which giant cell tumor may be confused are hemangioma of the bone and chondroma. Chondroma usually may be excluded because of its rare occurrence in the spine. Hemangioma has the appearance of giant cell tumor when the neural arch or its processes are involved. Hemangioma of the vertebral body, however, has a very characteristic appearance (fig. 13).

Giant cell tumor may affect any portion of a vertebra, but in our cases it involved the neural arch or its appendages more frequently than it involved the vertebral body. Lewis [10] also found this to be true in the cases reviewed by him. Only 1 tumor occurred in the cervical region. The tumors occurred with equal frequency in the other regions of the spine. The roentgenogram may show a rarefied lesion which reduces the portion of bone involved to a barely visible shadow (fig. 5). In the sacrum the margins are usually clearcut (fig. 6). The trabeculations characteristic of giant cell tumor in long bones may be present and may indicate a healing reaction. The typical expansile trabeculated type of tumor is best seen when the lesion involves a transverse or a spinous process. A tumor of the neural arch may go into the spinal canal and may be very difficult to detect by roentgen examination. Giant cell tumor involving the body of a vertebra is very likely to cause destruction with collapse (fig. 7). Clearcut concave edges can be seen. Figure 7 also illustrates the nature of the shadow visible in the soft tissues. No trabeculations are visible, yet it is clearly seen that this is an expansile, noninfiltrating type of tumor. Figure 8 shows the absence of the shadow in the soft tissues after surgical intervention and the healing reaction after roentgen therapy.

Giant cell tumor of the spine, in spite of its benign character, may cause death. Of the 14 patients, 9 recovered. The causes of death in 3 cases were damage to the spinal cord, invasion of the inferior vena cava and hemorrhage. In 1 case the tumor had infiltrated the soft parts extensively at the time the patient was last seen. In the remaining case the patient died from another cause before the giant cell tumor had healed.

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10. Lewis, D.: Primary Giant Cell Tumor of the Vertebrae, J. A. M. A. **83**:1224 (Oct. 18) 1924.

Fig. 5.—Giant cell tumor of the spine. The roentgenogram shows an extensive process of rarefaction, involving chiefly the third and fourth lumbar vertebrae. The fourth lumbar vertebra is almost entirely destroyed. The third lumbar vertebra shows only as a poorly defined shadow. A portion of the neural arch of the second lumbar vertebra is also destroyed. (Case of Dr. B. S. Putts, Erie, Pa.)

Fig. 6.—Giant cell tumor of the sacrum. The roentgenogram shows a rarefied area in the upper right half of the sacrum. The margins are clearcut, and faint trabeculations are visible. (Case of Dr. G. E. Bennett, Baltimore.)

Fig. 7.—Giant cell tumor involving the cervical vertebrae. The roentgenogram shows almost complete destruction of the body of the fourth cervical vertebra, with collapse and partial destruction of the bodies of the third and the fifth cervical vertebrae. There is also an expansile nontrabeculated mass in the prevertebral region pushing the larynx and trachea anteriorly. (Case of Mr. G. R. Girdlestone, F.A.C.S., Oxford, England.)

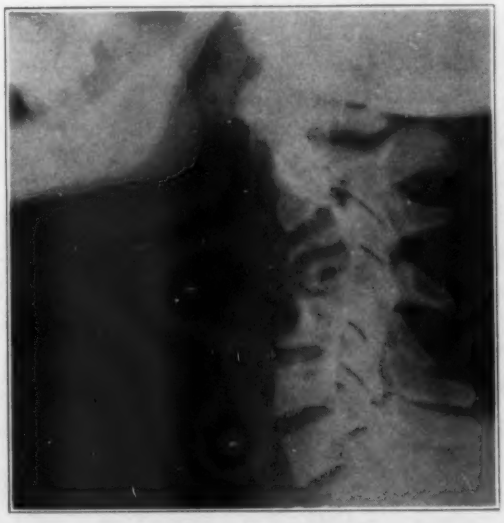

Fig. 8.—Giant cell tumor seen in figure 7, eleven months later. The tumor has been treated by curettage followed by irradiation. Notice the disappearance of the mass in the soft tissue and the healing reaction in the involved vertebrae.

Giant cell tumor may be diagnosed from the roentgenograms and treated with roentgen irradiation. In some cases operative procedures are necessary in order to relieve compression of the spinal cord or to stabilize the spinal column and prevent compression. An "aspiration biopsy" can be done and is not contraindicated in doubtful cases.

Bone Cysts.—In view of the relative frequency of giant cell tumor of the spine, one would expect bone cysts to be more common in this location. This, however, is not the fact. Multiple involvement of the spine, with bone atrophy and cyst formation, occurs as part of the syndrome of generalized osteitis fibrosa. There were 5 instances of such lesions. In 2 of these cystic lesions of the spine complicated the generalized skeletal deformity. In both of these cases pain in the back of increasing severity, was followed by signs of compression of the spinal cord. The roentgenologic picture showed diffuse atrophy of bone, bending deformities of the spine (most commonly kyphosis and scoliosis) and rarefaction and expansion of the bodies of one or more vertebrae or of a portion of the neural arch. In 3 other cases of generalized osteitis fibrosa demineralization and bending deformity of the spine were not accompanied by formation of the cysts.

No histologically verified solitary bone cysts of the spine, such as are commonly found in the shaft of the long bones in children, were recorded in this series. There was 1 such cyst occurring at the sacroiliac joint. In another instance a patient had been previously operated on for benign giant cell tumor, and at a second operation a similar lesion which had undergone cystic change was found above the original site. Microscopically this appeared to be a giant cell variant of the bone cyst. The absence of typical bone cysts in association with tumors of the spinal column lends support to the opinion that the usual bone cyst of the long bones is a benign giant cell tumor which has undergone healing. The failure of such a healing reaction to follow giant cell tumors of the vertebrae is explained by the cancellous structure of the vertebrae and by the absence of a well defined cortex of compact bone. The less rapidly growing giant cell tumors may take on a histologic character which justifies their classification as giant cell variants of the bone cyst, but active giant cell tumor tissue is rarely absent.

Osteochondroma.—Benign exostoses, which are so common in the remainder of the skeleton, are next in frequency. There were 10 of these in this series. Two were multiple exostoses affecting the remainder of the skeleton as well; the other 8 were all solitary lesions. With 2 exceptions the tumors arose from the neural arch or from one of its processes. In 3 cases the tumor projected into the spinal canal and gave rise to the symptoms of compression of the spinal cord. Case 4 is an instance of intraspinal osteochondroma.

CASE 4.—A woman complained of pain in the left leg present for eight years and of limping present for six months. There was tenderness in the lumbosacral region. Roentgen examination in November 1933 showed a dense mass, with a regular outline, filling the left side of the spinal canal at the level of the fifth lumbar vertebra (fig. 9). In December an osteochondroma was removed from the spinal canal. The patient was well on discharge from the hospital. Follow-up was not possible.

The roentgenologic picture of this tumor is typical of osteochondromas elsewhere. The more cartilaginous tumors might be confused with giant cell tumor. Such a condition is shown in figure 10. This tumor was irradiated and cartilaginous tissue was replaced by bone.

Fig. 9 (case 4).—Intraspinal osteochondroma, showing a dense mass filling the left side of the spinal canal at the level of the fifth lumbar vertebra. (Case of Dr. L. Y. Dryenforth, Jacksonville, Fla.)

One of the 10 patients died as a result of damage to the spinal cord. Excision is required only for those tumors presenting symptoms.

There was in the series 1 nucleus pulposus protruding into the spinal canal. This nucleus pulposus had become calcified and was shown in the roentgenogram as a dense rounded mass 1.5 cm. in diameter. Compere and Keyes [11] mentioned calcification of the extruded nucleus pulposus in their studies on the intervertebral disk.

11. Compere, E. L., and Keyes, D. C.: Roentgenological Studies of the Intervertebral Disc: Discussion of Embryology, Anatomy, Physiology, Clinical and Experimental Pathology, Am. J. Roentgenol. **29**:774, 1933.

Chondroma.—Camp, Adson and Shugrue [12] stated that chondroma of the spinal column is rare. In this series there was but 1 chondroma which was examined microscopically (case 5).

CASE 5.—A white man aged 23 complained of pain in the lower part of the back, difficult urination and constipation, present for four months. Rectal examination disclosed a mass anterior to the sacrum. Roentgen examination (film not available) four months after the onset was reported as showing a "diffuse shadow" in the sacral region. Seven months after the onset a colostomy was performed for intestinal obstruction. The patient died four and one-half years after the onset, and postmortem examination revealed a large, smooth encapsulated tumor arising from the sacrum and projecting into the pelvis but not obstructing the intestine. The microscopic diagnosis was chondroma.

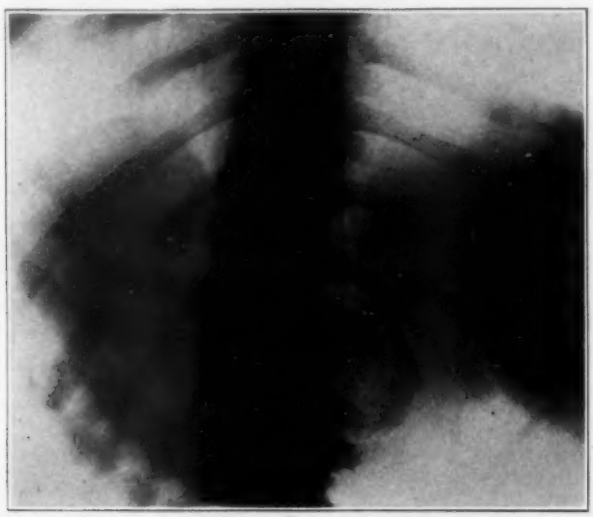

Fig. 10.—Osteochondroma involving a transverse process of the first lumbar vertebra. The tumor is well circumscribed and contains fine trabeculations. (Bone Registry American College of Surgeons no. 21.)

We cannot be sure of the diagnsois. No sections are available, and it is well known that chondrosarcoma and chordoma may be mistaken for chondroma. Examination of 2 other patients with tumors which are included in this group showed large rarefied areas in the sacrums, with cleancut margins. In neither case was the diagnosis proved by microscopic examination, and it may well be that the growths were giant cell tumors and not chondromas. Their slight response to irradiation

12. Camp, J. D.; Adson, A. W., and Shugrue, J. J.: Roentgenographic Findings Associated with Tumors of the Spinal Column, Spinal Cord, and Associated Tissues, Am. J. Cancer **17**:348, 1933.

suggests that they were chondromas. The patient whose condition is illustrated in figures 11 and 12 was under treatment with roentgen therapy for nine years. During this time the tumor showed an increase in size. It gives the impression of a chondroma.

Fig. 11.—Chondroma of the sacrum. The roentgenogram shows a well circumscribed, markedly trabeculated tumor involving the upper right half of the sacrum and extending over into the adjacent ilium.

Fig. 12.—Chondroma seen in figure 11, nine years later. The tumor was irradiated. Notice the extension of the tumor into the pelvis and into the adjacent ilium.

The absence of a certain diagnosis of chondroma for any growth in this series emphasizes the rarity of this tumor in the spine. A tumor displaying a roentgen picture of this type should be diagnosed as giant cell tumor. Irradiation should be tried, but it is less effective as a rule than for giant cell tumor.

Hemangioma.—Bucy and Capp[13] have contributed an excellent article on primary hemangioma of bone. They pointed out that when the vertebral bodies are involved vertical striations are produced which form an easily recognized roentgenologic picture (fig. 13). When a hemangioma involves a flat bone, such as the sacrum, a marked sunray effect is produced in the periosteal zone. This periosteal reaction is so marked and so regular that it may be distinguished from the somewhat similar picture of sclerosing osteogenic sarcoma in the same region. They also stated that the affected bone does not collapse and produce pain but that the first symptoms are those of compression of the spinal

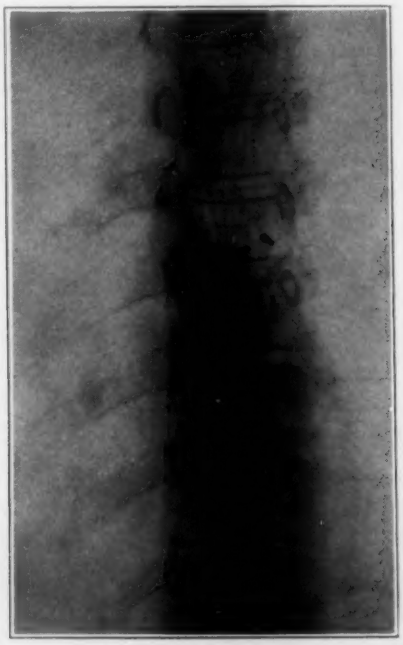

Fig. 13 (Bone Registry American College of Surgeons no. 940).—Multiple hemangioma of the vertebral bodies. The roentgenogram shows vertical striations in the bodies of the third, the fifth and the sixth thoracic vertebrae. (Courtesy of Dr. P. C. Bucy and Dr. C. S. Capp.)

cord. The histories of the 2 hemangiomas in our series support this statement. One tumor affected the laminas; the other, the transverse process. The latter case is reported below.

Case 6.—A white man aged 55 suffered pain in the left thigh for two and one-half years and loss of control of the bladder for three and one-half months. Saddle anesthesia and hyperactive reflexes were present. The Queckenstedt test

13. Bucy, P. C., and Capp, C. S.: Primary Hemangioma of Bone with Special Reference to Roentgenologic Diagnosis, Am. J. Roentgenol. **23**:1, 1930.

gave positive results. Roentgen examination in September 1927 revealed an expansile trabeculated tumor of the left transverse process of the first lumbar vertebra. A diagnosis of giant cell tumor was made, and at operation a hemorrhagic tumor involving the left transverse process and pedicle of the first lumbar vertebra was found. The tumor was removed with the curet. Microscopic examination revealed a cavernous hemangioma of bone.

It is interesting to note that the roentgen picture in case 6 was that of an expansile, trabeculated tumor resembling giant cell tumor (this emphasizes the variability of the roentgen pictures produced by hemangiomas involving the vertebral column). The histologic picture is almost invariably that of cavernous angioma, and the tumor responds readily to irradiation. Laminectomy, of course, is indicated when there are signs of compression of the spinal cord.

The small number of hemangiomas of bone in this series is not a true indication of its frequency. This indicates, instead, how infrequently symptoms are produced. Bucy and Capp stressed this point in their article, citing the work of Töpfer.[14] Töpfer in 2,154 autopsies found hemangiomas of the vertebral bodies in 257 instances (11.4 per cent); there were multiple growths in 34.

Only 1 angioma arising outside the spine and producing osseous changes was found. It arose in connection with the dura. The roentgenogram was reported as showing "a bulging of the bony framework of the cervical spinal canal." At operation an extradural hemangioma was disclosed which caused the laminas on the left side to bulge laterally and dorsally.

MALIGNANT PRIMARY TUMORS OF THE SPINAL COLUMN

Malignant primary tumors of the spinal column are less common than benign growths. There are but two types: osteogenic sarcoma and chordoma. Osteogenic sarcoma includes chondrosarcoma and the osteolytic and sclerosing types of sarcoma.

Chondrosarcoma.—There were 8 cases of chondrosarcoma of the spine. In 3 the tumor was single and primary; in 2 the growths were multiple but behaved like primary tumors; and in the remaining cases the sarcomatous change occurred in multiple exostoses (2 cases) or in Paget's disease (1 case). Excluding consideration of the time of appearance of the secondary chondrosarcomas, the average age of the patient at the onset was approximately 25 years. In 2 cases the only symptom was pain in the back, in 3 pain in the back was followed by symptoms

14. Töpfer, D.: Ueber ein infiltrierend wachsendes Hämangiom der Haut und multiple Kapillarektasien der Haut und inneren Organe: Zur Kenntnis der Wirbelangiome, Frankfurt. Ztschr. f. Path. **36**:337, 1928.

of pressure on the spinal cord, in 1 these symptoms preceded the pain in the back. Detailed histories were not available in the 2 remaining cases. In 5 cases death occurred from three months to three years after the onset. One patient is living seven years after the onset. The tumor is growing slowly at the present time. Two patients have not been traced. The tumors occurred in all portions of the spine. Cases 7, 8 and 9 illustrate the varying types of chondrosarcoma.

CASE 7.—*Single primary lesion.*

A white man aged 35 complained of pain in the back following an injury in May 1935. Roentgen examination of the spine in September revealed no abnormality, but further examination in December showed partial destruction of the body of the ninth thoracic vertebra with a faint paravertebral fusiform shadow

Fig. 14 (case 7).—Primary chondrosarcoma of a thoracic vertebra. The roentgenogram shows destruction of the body of the ninth thoracic vertebra without any appreciable collapse. A faint paravertebral fusiform shadow is visible. (Case of Commander H. E. Ragle [MC], U. S. Navy, Washington, D. C.)

(fig. 14). Spastic paralysis of the lower extremities developed in February 1936. In March a hemathorax was discovered, and tubercle bacilli were found in the sputum. Tuberculosis of the spine was considered the probable diagnosis. A roentgen examination at this time revealed an increase in the paravertebral shadow. The patient died in November, and at postmortem examination the region extending from the eighth thoracic vertebra to the tenth was found to be the site of a chondrosarcoma which had destroyed the spine and the spinal cord and had metastasized to the lungs.

CASE 8.—*Multiple primary lesions.*

A white girl aged 14 complained of difficulty in walking present nine months and of pain in the back and inability to flex the muscles of the neck present for one month. This condition progressed to a flaccid paralysis of both lower extremi-

ties. There was tenderness over the sixth thoracic vertebra. Roentgen examination in July 1931 revealed paravertebral spotty calcified areas in the upper dorsal region (fig. 15). Laminectomy at this time disclosed nodular cartilaginous masses external to the laminas and within the spinal canal. The patient died in November. Permission for autopsy was not obtained.

In a case similar to case 8 an autopsy was performed and multiple cartilaginous tumors were found affecting almost the entire skeleton. Figure 16 is a photograph of the lesion as seen at autopsy. It is probable that a roentgenogram in this case would have simulated that in case 8 (fig. 15). These 2 cases are peculiar in that multiple tumors arose simultaneously and were apparently not secondary changes occurring in preexisting multiple exostoses.

Fig. 15 (case 8).—Primary chondrosarcoma of the upper thoracic spine with multiple lesions. The roentgenogram shows paravertebral, spotty calcified shadows. (Case of Dr. George Armstrong, Ottawa, Ontario, Canada.)

CASE 9.—*Secondary sarcomatous change in a preexisting multiple lesion.*

A white woman aged 41 had had multiple exostoses as long as she could remember. Pain in the back had been present for three years and a palpable mass in the lumbar region for one year. Roentgen examination in May 1921 revealed the shadow of a mass in the soft tissues in the right lumbar region, containing many irregular dense areas (fig. 17). Roentgen examination of the rest of the skeleton revealed benign exostoses of the tibia, the fibula, the femur, the radius and the ulna, with the characteristic deformity of the radius and the ulna. Exploration of the lumbar mass in August disclosed a cartilaginous cystic tumor, with many calcified areas. Radium was used postoperatively. The patient died in June 1923, and at autopsy a chondrosarcoma weighing 8 Kg. was found in the lumbar region with metastases to the liver and the lung.

Fig. 16.—Primary chondrosarcoma of the spine with multiple lesions. The photograph of the spine at autopsy shows multiple cartilaginous nodules in the paravertebral region of the thoracic spine.

Fig. 17 (case 9).—Chondrosarcoma of the spine secondary to benign exostoses. The roentgenogram shows a faint paravertebral mass lateral to the third, fourth and fifth lumbar vertebrae. Irregular dense areas are visible within the tumor.

Osteogenic Sarcoma.—Four osteolytic sarcomas and 4 sclerosing sarcomas are included in the present series. Two sarcomas of the osteolytic type were superimposed on Paget's disease. The average age of the patients was 25 years, excluding those with sarcomas complicating Paget's disease. The outstanding symptoms were those of pain in the back or pain at the nerve roots, which was frequently followed by compression of the spinal cord. All of the sarcomas terminated fatally, with an average duration of life of twenty-one months. With the exception of the tumor in 1 case of Paget's disease, in which the sarcomatous change extended throughout the length of the spine, all the growths arose in the sacrum or in the lumbar vertebrae.

Figures 18 and 19 contrast the roentgenographic changes associated with sclerosing and osteolytic sarcoma respectively. The sclerosing type (fig. 18) may be confused with hemangioma in the sacrum, but with hemangioma the sunray effect in the periosteal zone is usually more regular and more pronounced. With osteolytic sarcoma (fig. 19) a diffuse destructive process with irregular invasive margins is seen. Osteolytic sarcoma might be confused with giant cell tumor (fig. 6). When the sclerosing type of sarcoma extends into the soft parts, bone is produced. This is a conclusive finding in the roentgenogram (fig. 20).

High voltage roentgen therapy was given to 5 of the patients with osteolytic and osteosclerosing sarcoma. Life was not prolonged, but pain was relieved. Roentgen therapy was employed in 1 case of chondrosarcoma of the sacrum (single primary lesion), and the patient is alive six years after onset. Radium was implanted during the treatment of 1 secondary chondrosarcoma (sarcoma complicating multiple exostoses), and the patient died two years after the beginning of the treatment. Roentgen therapy is the treatment of choice for osteogenic sarcoma of the spine.

Chordoma.—Chordoma has been frequently reported in the literature. In 1935 Mabrey [15] gathered 150 cases from the literature. Eighty-seven of the chordomas in his cases were sacrococcygeal, 49 were cranial and the remaining 14 were distributed elsewhere along the vertebral column. Ribbert [16] in 1894 named the tumor. Most observers agree that the notochord, from which the tumor arises, is of entodermal origin. According to Mabrey's statistics, the age of greatest incidence of the sacrococcygeal tumors is from 40 to 60 years and of the spheno-occipital

15. Mabrey, R. E.: Chordoma: A Study of One Hundred and Fifty Cases, Am. J. Cancer **25**:501, 1935.

16. Ribbert, M. W. H.: Ueber die Ecchondrosis physalifora sphenooccipitalis, nach Untersuchungen von Hermann Steiner, Centralbl. f. allg. Path. u. path. Anat. **5**:457, 1894.

tumors is from 20 to 40 years. He also stated that the average duration of life for these patients is twenty-eight and a half months, the extremes of age being 4 months and 18 years.

Fig. 18.—Osteogenic sarcoma (sclerosing type) involving the sacrum and the adjacent ilium. The roentgenogram shows a sclerosing process which extends out into the soft parts in the form of radiating bony spicules.

Fig. 19.—Osteolytic osteogenic sarcoma of the sacrum. The roentgenogram shows rarefaction in the upper part of the sacrum, with irregular margins.

In the laboratory of surgical pathology there are records of 5 cases of chordoma. In 3 of these the tumor was sacrococcygeal, in 1 occipital and in the other cervical. The ages of the patients ranged from

26 to 71 years. The patients who had a tumor in the cervical or occipital region died from encroachment of the tumor on the central nervous system. A tumor in the upper part of the cervical region may produce nasopharyngeal or pharyngeal symptoms. One of the patients with sacrococcygeal tumor had lived nine years after onset when last seen. The tumor had been excised three times and had been treated with radium. Another patient with a growth of this type was living four years after the onset. The tumor had been twice excised and in spite of roentgen therapy was still growing and was considered inoperable. In the remaining case the tumor was twice excised, and at the second

Fig. 20.—Osteogenic sarcoma of the lumbar spine. The roentgenogram shows marked destruction and sclerosis of the body of the second lumbar vertebra, with dense areas visible in the surrounding soft parts. Notice the absence of collapse of the body of the second lumbar vertebra. The adjacent vertebrae also show destructive and sclerotic changes.

operation metastatic nodules were removed from the soft tissue of the forearm, the arm, the hip and the pectoral region. This patient was not traced after the last operation.

The roentgenogram usually shows destruction of bone, with the shadow of a tumor in the soft tissues (fig. 21).

The tumor is slow growing but malignant and kills by invasion of vital structures. Mabrey estimated that at least 27 per cent of the

growths metastasize. There were metastases from 2 tumors in our series, to the regional lymph nodes in 1 instance and to distant soft tissues in the other.

The microscopic picture is variable. Alezais and Peyron.[17] basing their studies on the histogenesis of the notochord in the embryo, distinguished three general types. The first and most primitive type of chordoma, according to their studies, should correspond to that stage in which the notochord is evaginated from the entoderm. They could, however, find no tumor corresponding to this stage. A second and more clearly differentiated type of chordoma would be formed by solid cords of polyhedral and globular cells with abundant granular cytoplasm. Some of the cells show vacuolation. In our series 3 chordomas

Fig. 21.—Chordoma of the sacrum. The roentgenogram shows destruction of the lower portion of the sacrum, with a large intrapelvic mass (from previously published case, Harmos, O., and Palmer, L. A.: Chordomata and Report of a Case, Virginia M. Monthly **62**:638 [Feb.] 1936).

were of this type (figs. 22 and 23). In the third stage these cells become increasingly vacuolated and a homogeneous intercellular mucinous matrix is produced. Two of the tumors in our series presented a microscopic picture corresponding to that of this adult type of chordoma (fig. 24).

Irradiation seems to have little effect on this type of tumor. Surgical excision may be attempted, but recurrence is the rule.

17. Alezais and Peyron: Sur l'histogènèse et l'origine des chordomes, Compt. rend. Acad. d. sc. **174**:419, 1922.

SYMPATHICOBLASTOMA (AND EWING'S SARCOMA)

No mention has been made of Ewing's sarcoma in the discussion of the primary malignant tumors of the vertebral column. The reason for this omission is found in the succeeding paragraphs.

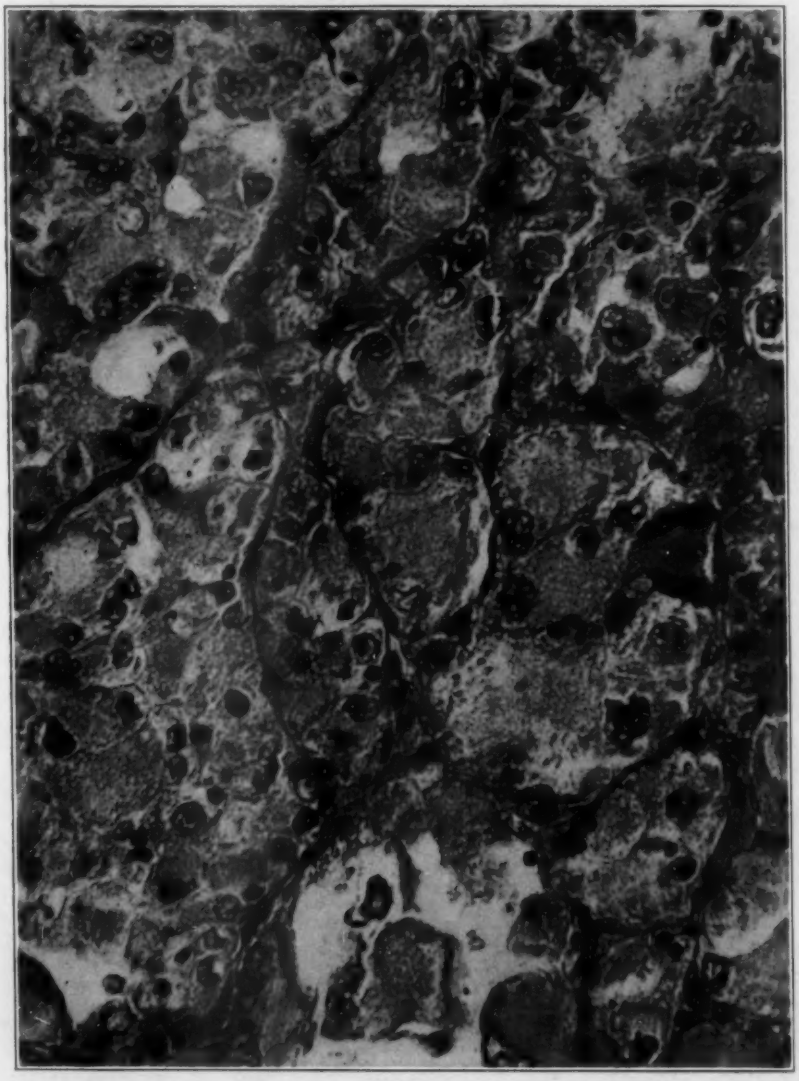

Fig. 22.—High power photomicrograph of a chordoma, showing large globular cells with abundant granular cytoplasm.

In a series of approximately 100 tumors involving the spinal cord, in the records of the department of neurosurgery of the Johns Hopkins

Hospital, there were 6 which affected bone and which on microscopic examination were found to be sympathicoblastomas. Records of 6 additional tumors of this type were found in the files of the laboratory of

Fig. 23.—High power photomicrograph of chordoma cells in the stage of vacuolization. (Case of Dr. W. S. Hastings, Fox Chase, Philadelphia.)

surgical pathology. These 12 tumors were types of sympathicoblastoma in all stages of differentiation. Summaries of the clinical histories of the cases are given at the end of the section describing the tumors.

The incidence of sympathicoblastoma in this series of spinal tumors was relatively high. This type of paravertebral tumor is not generally thought to complicate the diagnosis of neoplastic lesions about the vertebral column.

Fig. 24.—Low power photomicrograph of a chordoma in the adult stage. The chordomatous tissue is divided into lobules by fibrous septums. The lobules contain mucinous matrix and clusters of chordoma cells.

The average age of onset of these 12 sympathicoblastomas was 33 years, the extremes of age being 15 and 66 years. These ages appear

high, since sympathicoblastoma is generally a tumor of childhood and one of the commonest malignant tumors of that period. Scott and Palmer,[18] however, collected 32 cases of neuroblastoma arising from the sympathetic nervous system outside the adrenal medulla and found that the ages of the patients ranged from 1 month to 64 years. Schultz [19] tabulated 58 cases of benign ganglioneuroma and found that 26 of the tumors occurred in adults and 22 in children. The ages of 10 of the patients were not stated. Less clearly differentiated forms of neuroblastic tumor may also occur in adults (Wright;[20] Symmers;[21] Barnewitz;[22] Capaldi;[23] Busch;[24] Blumensaat[25]).

Both Schultz and Scott found the tumors more common among female than among male patients. In our series the incidence was equal in the two sexes.

The clinical histories in these cases were fairly uniform. The complaints were those of pain in the back, pain at the nerve roots or symptoms of compression of the spinal cord. Four patients showed symptoms of pressure on the spinal cord. In 6 others pain in the back preceded the onset of compression of the spinal cord. The remaining 2 had pain in the back as the only complaint. Pain at the nerve roots was an additional complaint of 5 patients. One expects, then, a tumor which destroys bone and presses on the spinal cord or on the nerve roots. Such is the case, as is seen by an examination of the roentgenologic, operative and postmortem evidence.

The roentgenogram showed a purely destructive lesion in 7 cases. In only 1 case was there a purely osteosclerotic lesion. In 3 cases osteolysis and osteosclerosis were both present. In addition, a paravertebral mass was visible in 4 of the roentgenograms. Figure 25 presents an example of osteosclerosis of the body of the tenth thoracic vertebra. In figure 26 a mass surrounded by a fairly well formed osseous

18. Scott, E., and Palmer, D. M.: Intrathoracic Sympathicoblastoma: Report of a Case, Am. J. Cancer **16**:903, 1932.

19. Schultz, O. T.: Tumors of Neurogenous Origin, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1926, vol. 8, p. 744.

20. Wright, J. H.: Neurocytoma or Neuroblastoma, a Kind of Tumor Not Frequently Recognized, J. Exper. Med. **12**:556, 1910.

21. Symmers, D.: A Recurrent Neuroblastoma of the Scapular Region, J. A. M. A. **60**:337 (Feb. 1) 1913.

22. Barnewitz: Zur Kenntnis des Neuroblastoma sympathicum, Frankfurt. Ztschr. f. Path. **26**:317, 1921.

23. Capaldi, B.: Zwei Fälle von Sympathikoblastom, Frankfurt. Ztschr. f. Path. **35**:83, 1927.

24. Busch, E.: On Ganglioneuroblastoma Sympathicum, Acta path. et microbiol. Scandinav. **5**:289, 1928.

25. Blumensaat, C.: Zur Kenntnis der Neuroblastome des Sympathicus beim Erwachsenen, Virchows Arch. f path. Anat. **269**:431, 1928.

Fig. 25 (case 16).—Sympathicoblastoma. The roentgenogram shows increased density of the body of the tenth thoracic vertebra with a paravertebral fusiform shadow. (Case of Dr. J. W. Riley, Oklahoma City.)

Fig. 26 (case 21).—Sympathicoblastoma. The roentgenogram shows destruction of the transverse process and pedicle of the third lumbar vertebra, with a paravertebral mass surrounded by a bony shell. (Case of Dr. H. R. Bohlman, Baltimore.)

shell is visible. This view also shows destruction of the left transverse process and pedicle of the third lumbar vertebra. Figure 27 is a roentgenogram of a postmortem specimen. The tumor stimulated reactive bone, thus producing the radiopaque area seen in the region of the spinal canal. These osteosclerotic changes may take place in the substance of the bone or may occur as a periosteal reaction.

The sympathicoblastomas in this series occurred in the thoracic or lumbar portion of the spine, with the exception of the tumor in case 10, which involved both the cervical and the thoracic region. Autopsy was

Fig. 27 (case 14).—Gangliosympathicoblastoma. The roentgenogram was taken of the postmortem specimen. It shows an osteosclerotic lesion in the region of the neural arch and spinal canal.

performed in only 50 per cent of the cases, but from correlation of the roentgenologic and the operative findings it is evident that there was a paravertebral mass (fig. 32) lying on the bodies of the vertebrae in 10 cases. One of the 10 tumors was a metastasis from the adrenal gland (case 15), but since it acted like a paravertebral tumor we have included it in this series. Of the 2 remaining tumors, 1 was intradural (case 18) and the other extradural (case 17). This intraspinal location is of frequent occurrence, since all the neuroblastic cells must migrate

peripherally from the primitive neural tube, and it is possible for a tumor to develop at any point between their site of origin and their destination.

Of the 10 tumors in the paravertebral region, 8 had extended into the spinal canal through an intervertebral foramen. In every instance bone was affected. These two features account for the clinical picture produced.

When seen at operation or at autopsy the tumors are friable, hemorrhagic and sometimes necrotic. Often they are fairly well circumscribed, though not encapsulated. One tumor (case 10) was described as having a polypoid appearance. There is a definite tendency of the tumor to extend in this serpiginous fashion. This is well shown by its extension into the spinal canal.

In this series of cases of sympathicoblastoma multiple metastases to bone occurred in 2 instances and a single metastasis to bone in 2 others. The lungs were involved in 4 instances. Metastasis to lymph

TABLE 4.—*(from Blacklock* [26]*)*

I—Sympathicoblastoma (all malignant)
(*A*) Undifferentiated—composed only of sympathogonia
(*B*) Differentiated
1—Composed of sympathogonia and sympathoblasts
2—Composed of ganglion cells in addition to more primitive cells (ganglio-sympathicoblastoma)
II—Ganglioneuroma (generally simple) [and benign*]
Composed only of mature ganglion cells

* Added by authors.

nodes occurred in 1 case. Death without metastasis occurred in 1 case from fatal damage to the spinal cord. Three patients are alive without metastasis. In the remaining 2 cases follow-up was not possible.

The histologic picture of these tumors is variable. The growth may show neuroblasts in any stage of differentiation. An understanding of the histology must be based on histogenesis. Table 4 is a simple classification based on histogenesis which was offered by Blacklock.[26] The term sympathicoblastoma was suggested by Bailey and Cushing [27] in 1926 for the undifferentiated tumors of the sympathetic nervous system.

The differentiation of the adult tissues of the sympathetic nervous system has been described by such observers as Bielschowsky,[28] Schultz and Scott. The neuroepithelium of the primitive neural tube gives

26. Blacklock, J. W. S.: Neurogenic Tumors of the Sympathetic System in Children, J. Path. & Bact. **39**:27, 1934.

27. Bailey, P., and Cushing, H.: A Classification of Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

28. Bielschowsky, M.: Neuroblastic Tumors of the Sympathetic Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1085.

rise to neuroblasts and glial cells. The neuroblasts of the sympathetic nervous system form sympathogonia. These are small cells with a round or oval hyperchromatic nucleus, scanty cytoplasm and at times delicate fibrils. As differentiation proceeds, the nuclei become larger and more

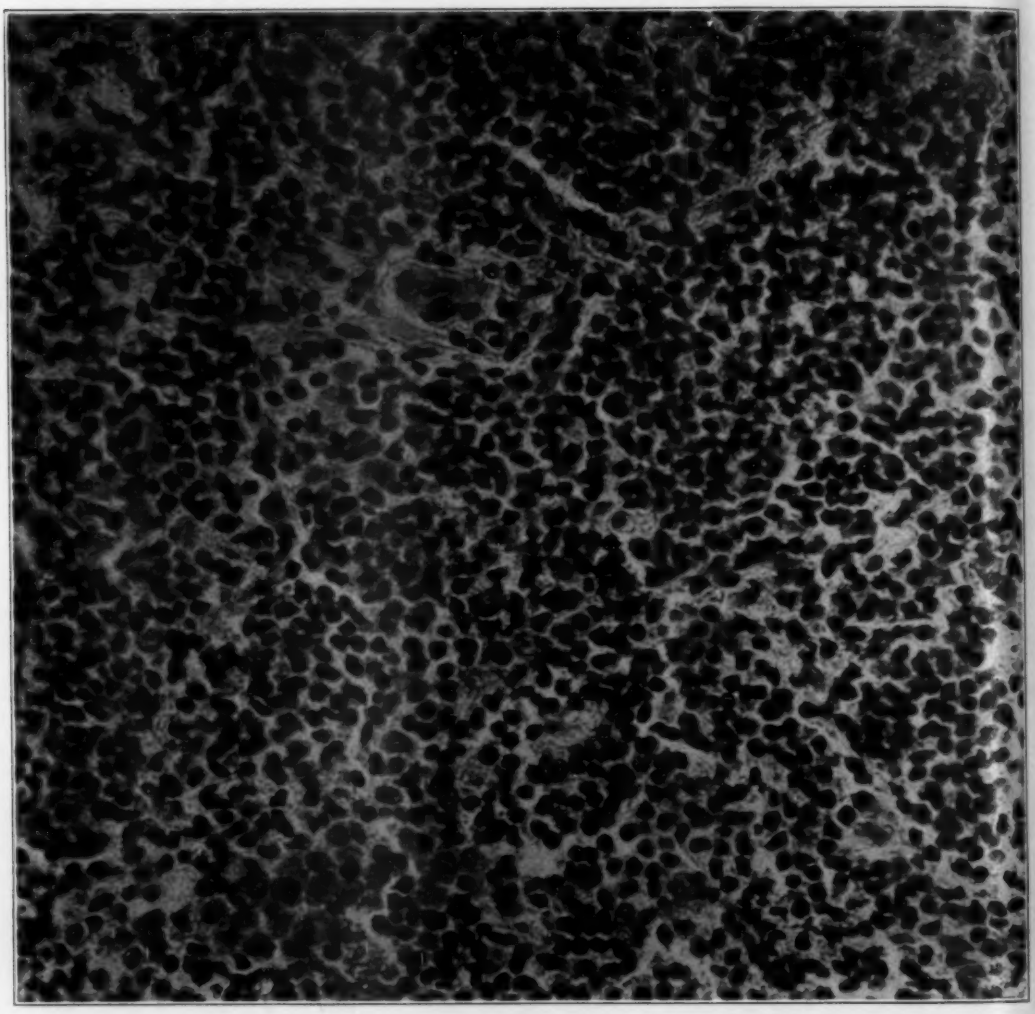

Fig. 28 (case 19).—High power photomicrograph of sympathicoblastoma, showing a cellular tumor consisting mostly of sympathogonia. A few sympathoblasts may be seen.

vesicular and the cytoplasm becomes more abundant. The cytoplasmic processes or the fibrils become prominent features. The cells are then sympathoblasts. As the cells approach the adult form, the nuclei are

enlarged and show large nucleoli; the cytoplasm increases and acquires Nissl granules. The cells are then ganglion cells.

The pheochromocyte of chromaffin tissue also differentiates from the sympathogonia. However, no tumors of this type occurred in the present series.

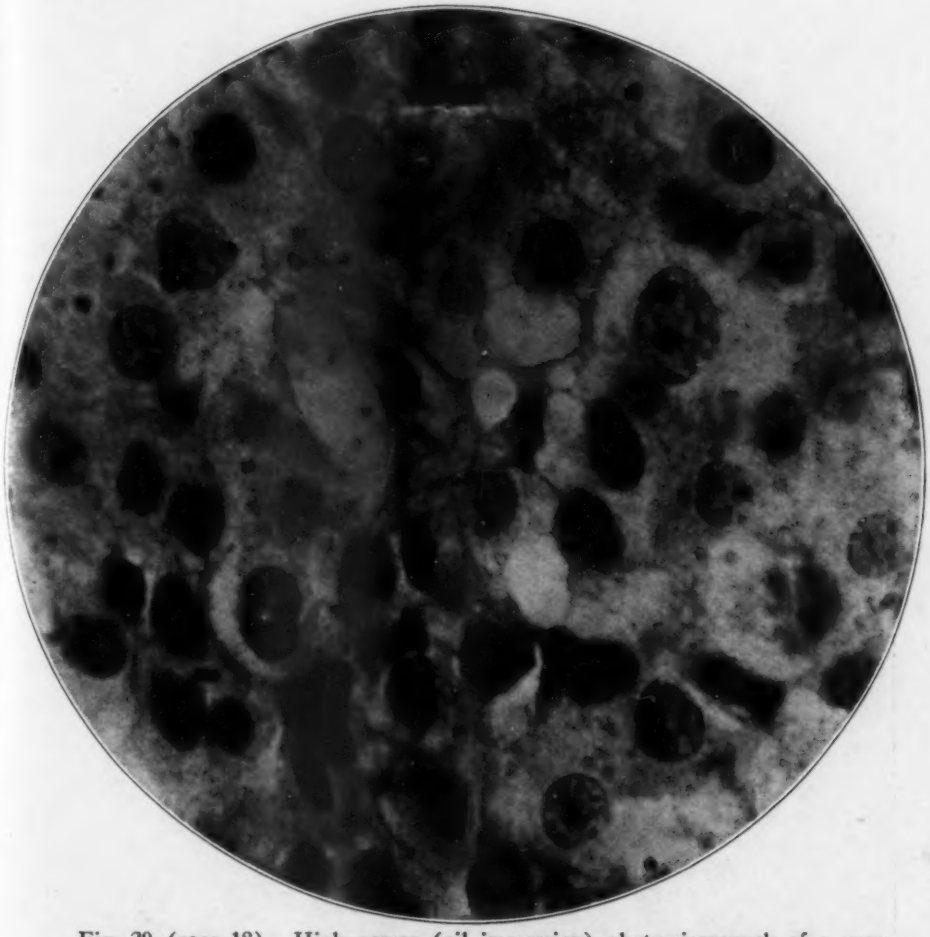

Fig. 29 (case 18).—High power (oil immersion) photomicrograph of a sympathicoblastoma, showing sympathoblasts with large vesicular nuclei and cytoplasm in processes.

A sympathetic neural tumor may arise from any of the types of cell described in the differentiation of the neuroblast. Sympathogonia and sympathoblasts are commonly present in the same tumor. All three types may be present (gangliosympathicoblastoma). Sympathogonia predominate in the undifferentiated sympathicoblastoma (fig. 28). Rosettes are few and are often indicated only by clumps or balls of cells (Blacklock).

When sympathoblasts are present in abundance, fibrils are usually a prominent feature (fig. 29). Rosettes are often present. The intermingling of the two types of cells, sympathogonia and sympathoblasts, forms a microscopic picture characteristic of the differentiated sympathicoblastoma (fig. 30). Well formed rosettes were not numerous

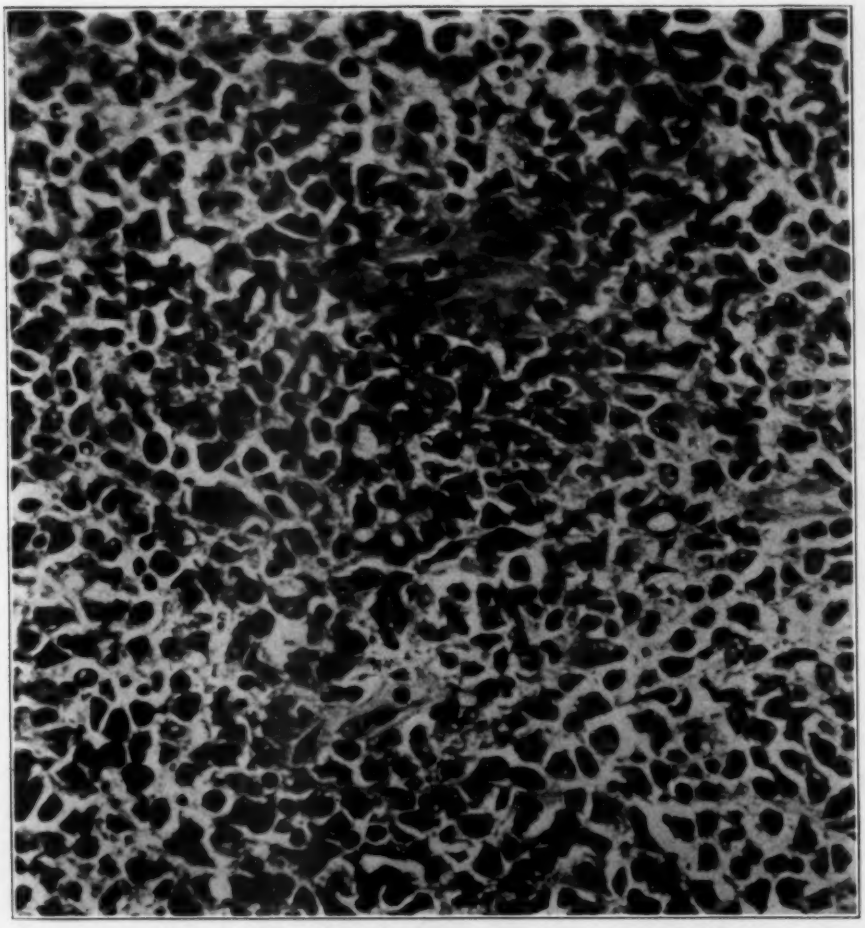

Fig. 30 (case 21).—High power photomicrograph of a sympathicoblastoma, showing sympathogonia and sympathoblasts.

in any of these tumors. Mitotic figures though present were not numerous.

When the adult ganglion cell is present, the tumor is easily identified (fig. 31). The gangliosympathicoblastomas usually contain less differentiated cells as well. In this section reactive bone and fibrosis were marked features.

The reaction of the sympathicoblastomas to treatment remains to be considered. Table 5 shows the duration of life of the patients and the type of treatment for this condition. Excision of the tumor fol-

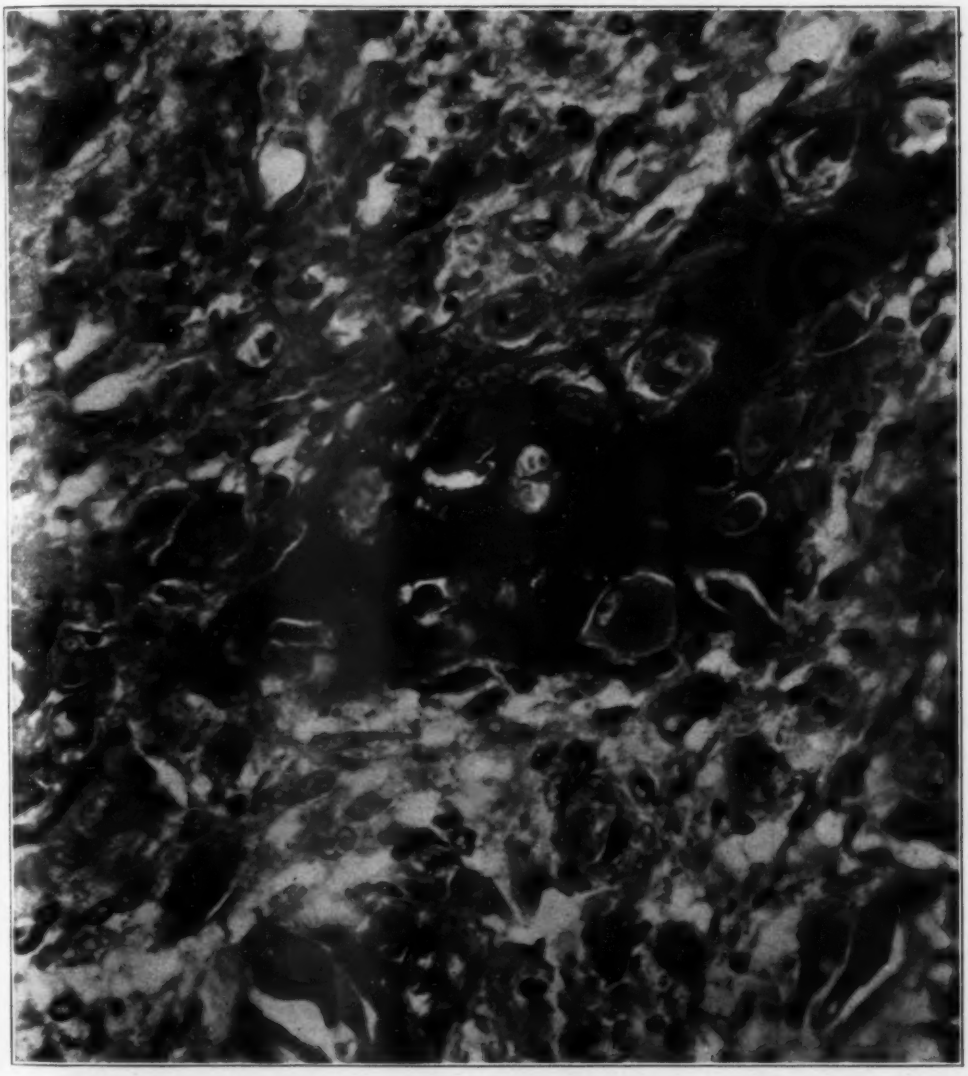

Fig. 31 (case 14).—High power photomicrograph of a gangliosympathicoblastoma, showing adult ganglion cells some of which are embedded in bone.

lowed by irradiation is apparently the treatment of choice. The relatively long duration of life in case 14, in which the patient received no treatment, is explained by the fact that the tumor in that case was

of a more clearly differentiated and less malignant form than were the other tumors.

Table 5 indicates that sympathicoblastoma is radiosensitive. The patient in case 17 was well without recurrence of symptoms seven years after the operation. Irradiation was given postoperatively. Stewart [29] and also Colville and Willis,[30] have observed that neuroblastoma (sympathicoblastoma) responds to irradiation. This radiosensitivity is a characteristic of two other neuroblastic tumors, retinoblastoma (Moore [31]) and medulloblastoma (Cutler, Sosman and Vaughan [32]), both of which resemble sympathicoblastoma in histologic appearance.

Ewing's Sarcoma.—No tumors were found in this series which could unquestionably be diagnosed as Ewing's sarcoma of the spine. The remarkable similarities between this tumor and sympathicoblastoma

TABLE 5.—*Duration of Life of Patients and Type of Treatment in Cases of Sympathicoblastoma*

Case No.	Duration of Symptoms Prior to Treatment, Months	Duration of Life After Treatment, Months	Treatment	Result
12	..	72	Excision; irradiation	Patient died
17	5	84	Excision; irradiation	Patient well 1938
16	18	43	Excision; irradiation	Patient died
10	6	42	Excision	Patient died
13	2	21	Excision; irradiation	Patient died
11	6	12	Excision; irradiation	Patient died
19	1	7	Excision	Condition of patient improved 1937
21	18	4	Excision	Condition of patient improved 1937
15	6	0	None	Patient died
14	60	0	None	Patient died
20	5	..	?	Patient died
18	8+	?	Excision	No follow-up

account in some measure for this difficulty. The microscopic picture of Ewing's sarcoma and that of sympathicoblastoma are strikingly similar, and by the ordinary staining methods differentiation between the two is difficult. The reticulum cell variant of Ewing's sarcoma is not unlike a sympathicoblastoma in which sympathoblasts predominate. In addition, both types of tumor may respond to high voltage roentgen therapy. Both types of tumor also have a tendency to metastasize to one or more bones, to the lungs or to the lymph nodes.

29. Stewart, F. W.: Radiosensitivity of Tumors, Arch. Surg. **27**:979 (Dec.) 1933.

30. Colville, H. C., and Willis, R. A.: Neuroblastoma Metastases in Bones, with a Criticism of Ewing's Endothelioma, Am. J. Path. **9**:421, 1933.

31. Moore, R. F.; Stallard, H. B., and Milner, J. G.: Retinal Gliomata Treated by Radon Seeds, Brit. J. Ophth. **15**:673, 1931.

32. Cutler, E. C.; Sosman, M. C., and Vaughan, W. W.: The Place of Radiation in the Treatment of Cerebellar Medulloblastoma: Report of Twenty Cases, Am. J. Roentgenol. **35**:429, 1936.

The frequency with which multiple bone metastases are noted soon after the appearance of a primary Ewing sarcoma of bone has often been described as a characteristic of this tumor. The first clinical evidence of a sympathicoblastoma may be a metastatic lesion in the skull. Coleville and Willis observed the case of an 8 year old child who previous to death presented a typical picture of Ewing's sarcoma of the femur. The age, history, roentgen findings, observations at biopsy and response to irradiation were all consistent with this diagnosis. The child died five months after onset, and at autopsy a neuroblastoma of the adrenal was found, with multiple metastases to bone.

Since these two tumors are so similar, the question arises as to whether some of the tumors in our series diagnosed as sympathicoblastomas were not Ewing sarcomas of the spine. To be considered against this theory is the fact that these growths were paravertebral in origin, whereas Ewing's sarcoma usually begins in the bone proper. In general, the microscopic structure of the individual tumors is more variable than that of Ewing's sarcoma and corresponds to the structure of tumors of the sympathetic nervous system described in the literature, as well as to the structure of those studied in this laboratory. Because roentgenologic changes in the complex bony structure of the spine are not comparable to those in other bones, the roentgenologic changes characteristic of a Ewing sarcoma in the long bones do not aid in distinguishing between these two tumors in the spine.

On the other hand, the suggestion has been offered by some authors (Colville and Willis) that Ewing's sarcoma of bone is in some cases a metastasis from a sympathicoblastoma. Such mistakes in clinical diagnosis undoubtedly occur. The fact that a Ewing sarcoma may arise as a primary tumor of bone, however, is established by those cases in which the patient has been permanently cured by radical removal of the affected bone. Records of 5 patients with Ewing's sarcoma remaining well for periods varying from five to ten years after such surgical treatment are recorded in this laboratory.

From the considerations herein presented, however, it is apparent that further investigations are necessary, particularly in regard to the staining reactions of Ewing's sarcoma and of sympathicoblastoma, in order to differentiate clearly these two forms of malignant growths.

The clinical histories of 12 cases of sympathicoblastoma are here reported (case 10 to case 21, inclusive).

CASE 10.—A white youth aged 16 complained of pain in the right arm present for six months and of pain in the left arm present for one week. Examination revealed weakness and hypoesthesia of both arms, tenderness in the cervicodorsal region and positive results from a Queckenstedt test. Roentgen examination in March 1933 was reported as showing no abnormalities. At operation in the same month an extradural nonencapsulated tumor extending from the fourth to the

seventh cervical vertebra was removed. The tumor had eroded the intervertebral foramen as it passed out into the neck. The condition of the patient improved after the operation, but symptoms of compression of the spinal cord again developed in the fall of 1935. Roentgen examination in November 1935 revealed increased density in the bodies of the seventh cervical and first thoracic vertebrae, with slight destructive changes and a slight periosteal reaction. There also appeared to be a mass anterior to the vertebral bodies which displaced the trachea forward. Roentgen examination in February (fig. 32) revealed an increase in the size of the prevertebral mass. Laminectomy was again performed in February, but no tumor was found. The patient's condition did not improve, and he died of tracheal obstruction in September. At autopsy a friable hemorrhagic tumor was found overlying the bodies of the cervical vertebrae. Though it was not encapsulated, it was fairly well circumscribed, almost polypoid in appearance. The vertebral bodies were eroded and invaded. The tumor extended into the spinal canal and compressed the spinal cord. It encircled the esophagus and the trachea and extended downward into the upper mediastinum. The subclavian and jugular veins

Fig. 32 (case 10).—Sympathicoblastoma in the cervical region. The roentgenogram shows increased density of the bodies of the seventh cervical and first thoracic vertebrae, with slight destructive changes in the anterior portions of the bodies of these vertebrae. A paravertebral mass is visible which has displaced the trachea anteriorly. A laminectomy has previously been done.

were invaded. The lungs contained metastatic nodules. Microscopic examination revealed a cellular tumor invading muscle and divided into large alveoli by fibrous septums. The cells were almost entirely sympathogonia. Necrotic areas, rare, poorly formed rosettes and occasional mitotic figures were present.

Case 11.—A white woman aged 30 complained of pain in the back present for six months and of numbness of the legs and feet present for two weeks. On examination, tenderness was elicited over the sixth and seventh thoracic vertebrae and a partial spastic paralysis, with hypoesthesia, was present below the level of the seventh rib. Roentgen examination in December 1930 showed destruction and partial collapse of the body of the sixth thoracic vertebra and destruction of the spinous processes and the laminae of the thoracic vertebrae from the fifth to the seventh. At operation in the same month an extradural tumor was found destroying bone, pressing on the spinal cord and extending into the mediastinum.

The mass was partially removed. The patient's condition improved, but she returned in August 1931 complaining of pain in the back, radiating to the right breast, and of numbness of the fingers. Operation was again performed, but the tumor was inoperable. The patient received roentgen therapy postoperatively but died in November. Postmortem examination revealed a mass overlying the vertebral bodies from the fourth thoracic to the seventh. It had invaded and destroyed the body of the fifth thoracic vertebra. The spinal cord and the dura also had been invaded and the tumor had metastasized to the lungs. Microscopic examination revealed a cellular tumor composed mostly of sympathoblasts and divided by fibrous septums. Cytoplasmic processes were prominent. Occasional mitotic figures, poorly formed rosettes and clumps of sympathogonia with parallel nuclei were present.

Case 12.—A white youth aged 15 had an encapsulated tumor removed in November 1928. It had compressed the spinal cord at the level of the second and third thoracic vertebrae and had extended into the mediastinum. It had also caused partial paralysis. Roentgen therapy was given after the operation, but the tumor recurred and was removed again in 1931. In June 1932 pain developed at the neural roots at the level of the third thoracic vertebra, and paralysis was present below this level. Roentgen examination at this time showed a mass immediately to the right of the spine at the level of the fourth thoracic vertebra. The patient was again operated on, and a tumor was found which pressed on the spinal cord and extended into the neck and the upper part of the mediastinum. This tumor was partially removed. The patient's condition did not improve, and he died in October 1932. At autopsy a paravertebral mass was found in the upper thoracic region which had metastasized to other vertebrae, to a rib, to the femur and to the hypophysial region of the skull. Microscopic examination revealed a cellular tumor almost entirely composed of sympathogonia and divided by fibrous septums. Many clumps and balls of closely packed nuclei were present. The cytoplasm was scanty, and mitotic figures were rare.

Case 13.—A white woman aged 23 complained of pain in the right hip, extending down the thigh, present since September 1932. Examination revealed anesthesia of the outer side of the right foot and a tender mass to the right of the fourth and fifth lumbar vertebrae. Roentgen examination in April 1933 showed a destructive lesion involving the upper part of the right side of the sacrum and the right side of the fifth lumbar vertebra. In November the mass was removed, and roentgen therapy was given postoperatively. The patient died in August 1934, and at autopsy a huge tumor was found which had destroyed the right side of the sacrum, the right ileum and the lower lumbar vertebrae and had metastasized to the thoracic vertebrae, the sternum and the lung. Microscopic examination revealed a tumor composed chiefly of sympathoblasts, with well marked cytoplasmic processes. There were occasional mitotic figures and poorly formed rosettes.

Case 14.—A white man aged 42 complained of pain in the lumbar region present for five years, of difficult urination present for seven months and of paralysis of the left leg present for four months. Examination revealed tenderness in the upper lumbar region. Roentgen examination was reported to have produced negative results. The patient died in April 1923, and at autopsy a hemorrhagic osseous mass was found, which arose to the left of the first and second lumbar vertebrae. The tumor had destroyed bone in that region and had invaded and filled the spinal canal. Roentgen examination of the postmortem specimen showed an osteosclerotic process in the region of the spinal canal (fig. 27). Microscopic examination revealed adult ganglion cells scattered throughout the tissue. Reactive bone,

fibrosis and an occasional giant cell were present. Numerous fibrils were seen about some of the ganglion cells. Some of these cells were embedded in bone, and a few sympathoblasts were present. An occasional mitotic figure was seen (fig. 31).

Case 15.—A white man aged 45 complained of pain in the lower part of the back following an injury five months before and of pain in the chest and bloody sputum present for one month. A tumor had been noticed in the left axilla for one month. Roentgen examination revealed destruction of the left transverse process and of the left side of the body of the fourth lumbar vertebra. There were also osteolytic changes in the ribs and in the skull. At autopsy in October 1931 a tumor of the left adrenal medulla was found, with metastases to the spine, the ribs, the skull, the brain, the lymph glands and the lungs. Microscopic examination showed a cellular tumor composed principally of sympathoblasts, divided by fibrous septums into alveoli. Most of the nuclei were elongated and lay parallel to each other in small groups. An occasional mitotic figure was found, as well as an occasional poorly formed rosette.

Case 16.—A white man aged 29 complained of pain in the back following an injury eighteen months before and of gradually increasing symptoms of compression of the spinal cord ending in complete paralysis of both lower extremities three days before roentgen examination. There were sensory changes at the level of the eighth thoracic segment. Roentgen studies in September 1929 showed osteosclerosis of the body of the tenth thoracic vertebra, with a fusiform paravertebral mass (fig. 25). Laminectomy in the same month disclosed an extradural tumor adherent to the laminas of the ninth thoracic vertebra and pressing on the spinal cord. Roentgen therapy was employed postoperatively. The condition of the patient was improved by the operation. In June 1930 a hard mass above the left clavicle was noted, which seemed to be attached to the spine. Roentgen examination at this time revealed osteosclerosis of the body of the sixth cervical vertebra. The patient died in April 1933. Permission for autopsy was not obtained. Microscopic examination revealed a cellular tumor composed almost entirely of sympathoblasts and divided by numerous fibrous septums. The nuclei were large and vesicular, with large nucleoli. The cytoplasm, though not abundant, was well marked and extended into short processes. There were present a few groups of sympathogonia with parallel nuclei. No rosettes were seen. Mitotic figures were rare.

Case 17.—A white woman aged 17 complained of pain in the left leg present for five months and of weakness of the left leg, numbness of the left buttock and difficult urination present for six weeks. The fifth lumbar vertebra was tender, and there was a mass over the dorsum of the sacrum. Roentgen examination in April 1931 showed destruction of the laminas and transverse processes of the left sacral vertebrae from the second to the fifth. At operation in the same month an extradural tumor was found in the sacral canal which extended into the lumbar canal and out through the anterior sacral foramen. It was partially removed, and irradiation was given postoperatively. The patient was well in 1938, without recurrence of the symptoms. Microscopic examination revealed a cellular tumor invading muscle. Both sympathogonia and sympathoblasts were present. Cytoplasmic fibrils were present in abundance. Groups of deeply staining, elongated, parallel nuclei were frequent. No well formed rosettes were seen, and mitotic figures were rare.

Case 18.—A white man aged 47 complained of loss of control of the bladder present for eight months, numbness of the feet present for two months and difficult

walking present for one month. On examination, partial paralysis, with hypoesthesia of the lower extremities, and positive results of a Queckenstedt test were found. Roentgen examination was reported as showing "hypertrophic arthritis" (plates not available). In December 1924 an intradural nonencapsulated tumor extending from the eleventh thoracic vertebra to the third lumbar vertebra was partially removed. The lamina of the first lumbar vertebra was perforated by an irregular opening, and the neighboring laminas were thin and soft. The patient was discharged with his condition improved. Follow-up was not possible. Microscopic examination revealed a cellular tumor divided by fibrous septums. Sympathoblasts predominated in number over sympathogonia. Cytoplasmic processes were well marked and formed a network of fibrils. A few groups of parallel, hyperchromatic, elongated nuclei were seen. Mitotic figures were rare (fig. 29).

CASE 19.—A white woman aged 45 complained of pain in the back and at the roots of the spinal nerves present for four weeks and of increasing symptoms of compression of the spinal cord present for three weeks. The third and fourth thoracic vertebrae were tender, and there were sensory changes at the level of the sixth thoracic segment. No roentgenogram was taken. In October 1936 a nonencapsulated extradural tumor was removed. This tumor had pressed on the spinal cord and had extended into the mediastinum through a defect in the bony column at the level of the third and fourth thoracic vertebrae. The patient's condition was slightly improved in April 1937. Microscopic examination revealed a cellular tumor composed mainly of sympathogonia. A few poorly formed rosettes were seen. In some areas there were groups of elongated, hyperchromatic, closely packed nuclei lying parallel to one another. These groups sometimes formed balls or whorls of nuclei. Mitotic figures were rare (fig. 28).

CASE 20.—A man aged 24 complained of pain over the sacrum present for five months, followed by pain in the legs and numbness of the right foot. Roentgenoscopic examination showed a destructive lesion in the body of the fifth lumbar vertebra, without collapse, and destruction of the right transverse process. The patient died in June 1930. Microscopic examination (it is not known whether the tissue was obtained at operation or at autopsy) revealed a cellular tumor invading muscle. Sympathoblasts were present in excess. A network of fibrils was a prominent feature. No well formed rosettes were seen, but clumps of sympathogonia were present. Mitotic figures were scarce.

CASE 21.—A white woman aged 66 complained of pain in the lower part of the back present for one and one-half years. There was tenderness in the lumbosacral region. Roentgen examination in January 1937 showed destruction of the left transverse process and pedicle of the third lumbar vertebra and a paravertebral mass in that region, with an irregular bony shell (fig. 26). A biopsy was performed in the same month. Microscopic examination revealed a cellular tumor composed mostly of sympathoblasts. Large necrotic areas were present. Mitotic figures were rare (fig. 30).

GLIAL AND SHEATH TUMORS OF THE SPINAL CORD

Glial tumors and tumors of the neural sheath and of the meninges may in some cases be difficult to distinguish preoperatively from other neoplastic lesions of the spine. It has already been shown in the preceding discussion that some of the primary or paravertebral tumors of the spine may cause neurologic symptoms as the first and only complaint. As a rule, however, intramedullary tumors and benign tumors of the

nerve sheaths may be diagnosed by the fact that the neurologic features are prominent and that the changes in bone, if present, are either slight or characteristic. This does not apply to malignant tumors of this type or to certain varieties of glial tumors. The latter tumors are uncommon.

Perineurial Fibroblastoma (Neurinoma).—This tumor occurs in the spine with a frequency approximately equal to that of meningeal tumors, and each is more common in this region than is glioma. Perineurial fibroblastoma (neurinoma) occurs more frequently in the lumbar and the sacral region than in other parts of the spine. The benign form is a firm, encapsulated intradural or extradural tumor attached to a nerve root. It may or may not extend outside the spinal canal in hourglass fashion. It produces symptoms of compression of the spinal cord or of the cauda equina, often associated with pain at the nerve roots. Even when changes in bone occur, pain in the back is not a common complaint, though localized tenderness may be present. Camp, Adson and Shugrue pointed out that this tumor more commonly than any other glial or nerve sheath tumor produces changes in the vertebral column. According to their studies, the pedicle, the laminas and the body of the vertebra are eroded in the order mentioned. The transverse process may be eroded by an extraspinal portion of the tumor. Figure 33 shows erosion of the pedicles and laminas of the fifth lumbar vertebra. A lateral view in this case showed a circular defect 3 cm. in diameter at the right intervertebral foramen. The erosion caused by these benign tumors is smooth and must be distinguished from the destruction of bone produced by invasive tumors. Slight erosions are easily overlooked. Measurement of the spinal canal reveals changes in bone in a large number of the cases. Basing their studies on a series of tumors of the spinal cord, Elsberg and Dyke [33] were able by this method to detect changes in 42 per cent of 67 cases and in 70 per cent of 20 cases in which the tumors were between the tenth thoracic vertebra and the first sacral vertebra. A neurinoma may occasionally contain calcified areas which are visible in the roentgenogram, but this feature is much more characteristic of meningiomas.

In this series there were 8 benign neurinomas which produced changes in bone detected in the roentgenogram or at operation. No attempt was made with these or with any of the glial or nerve sheath tumors to detect slight changes by measurement of the spinal canal.

Sarcoma of a nerve sheath is not so clearly characteristic in the roentgenogram as is neurinoma. There were 4 such tumors in this

33. Elsberg, C. A., and Dyke, C. G.: Diagnosis and Localization of Tumors of the Spinal Cord by Means of Measurements Made on the X-Ray Films of the Vertebrae, and the Correlation of Clinical and X-Ray Findings, Bull. Neurol. Inst. New York **3**:359, 1934.

series, and in 2 of the cases pain in the back was a prominent complaint and preceded the symptoms of compression of the spinal cord. Destruction of bone, rather than smooth erosion, was produced in every case (fig. 34). Sarcoma of a nerve sheath is more common than meningeal sarcoma.

Meningeal Tumors.—Meningeal tumors occur more frequently in the thoracic and the cervical region than in other portions of the spine. The benign form is a firm, encapsulated intradural or extradural tumor attached to the meninges. It may occasionally have an extraspinal portion.

Fig. 33.—Perineurial fibroblastoma at the level of the fifth lumbar vertebra. The roentgenogram shows erosion of the laminas and of both pedicles of the fifth lumbar vertebrae, most marked on the right side. (Case of Dr. W. McL. Shaw, Jacksonville, Fla.)

There were 6 meningiomas in this series which were detectable in the roentgenogram by reason of gross changes in bone or calcification of the tumor. Pain in the back was not a feature. Erosion of bone is less commonly produced than it is by neurinoma. The benign tumors cause a smooth erosion of bone. Calcification, even ossification, is not uncommonly found with these tumors and may be present in sufficient amounts to show in the roentgenogram (fig. 35). Sarcoma of the

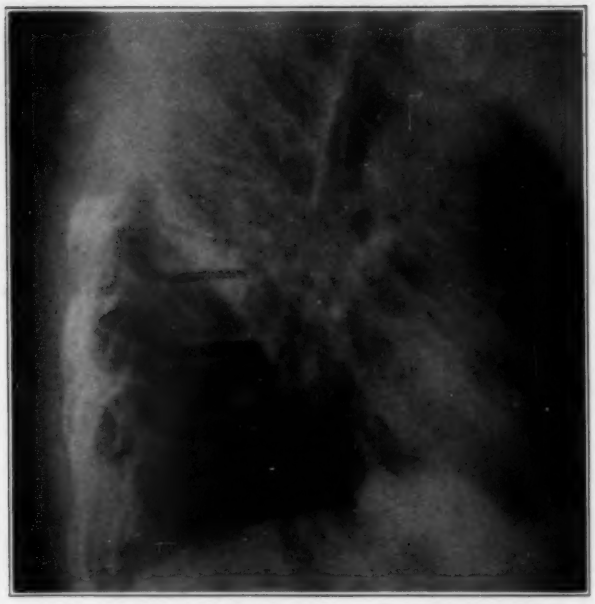

Fig. 34.—Sarcoma of the neural sheath involving a thoracic vertebra. The roentgenogram shows destruction, with partial collapse, of the body of the eighth thoracic vertebra. (Case of Dr. E. T. Wentworth, Rochester, N. Y.)

Fig. 35.—Meningeal fibroblastoma. The roentgenogram shows a calcified mass lateral to the fourth cervical vertebra which has destroyed the pedicle and transverse process in this region. (Case of Dr. A. Wilson Smith, Chicago.)

meninges causes an invasive type of destruction of bone. There was 1 such tumor in this series.

Multiple Neurofibromatosis.—In this neoplastic condition neurofibromas may form on all the spinal nerve roots and cause erosion of bone in the region of the intervertebral foramens (fig. 36). A paravertebral mass may be visible in the roentgenogram, together with underlying destructive changes in the bone. There were 2 cases of this condition.

Glial Tumors.—Intramedullary glioma is less common than nerve sheath tumor in the spine and rarely produces gross changes in bone.

Fig. 36.—Multiple neurofibromatosis. The roentgenogram shows a faint, well circumscribed lobulated mass in the left paravertebral region. Several of the pedicles of the thoracic vertebrae in this region are seen to be absent or eroded.

There were but 2 such intramedullary gliomas in this series. One caused a smooth erosion of the laminas, and the other was demonstrable in the roentgenogram because of calcification in the tumor itself.

There were 6 extramedullary glial tumors in this series which caused osseous changes. All these tumors may be classed as primitive, and all occurred below the level of the eleventh thoracic vertebra. There were 3 ependymomas. These tumors caused a smooth erosion of bone. There were 2 heterotopic astroblastomas (possibly unusual varieties of ependymoma), 1 of which caused an erosion of the laminas and the

other of which invaded and destroyed bone (fig. 37). The remaining tumor was a primitive neuroepithelioma (fig. 38) which occurred ventral to the sacrum, causing destruction of that bone.

In general, it may be said that the glial tumors which cause osseous changes are of the less differentiated, extramedullary type and that they occur in the lumbar and sacral regions.

TERATOID AND TERATOLOGIC TUMORS

Sacrococcygeal tumors are often grouped together. Ependymoma, chordoma, neuroepithelioma and giant cell tumor are sometimes described

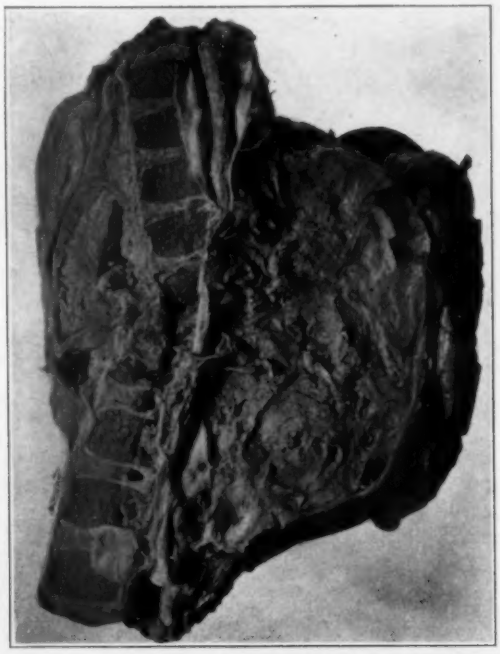

Fig. 37.—Astroblastoma in the dorsolumbar region. The photograph shows a longitudinal section of the lesion at autopsy. There is a large paravertebral mass dorsal to the spine and a smaller ventral mass. Six vertebrae are either partially or completely destroyed. At postmortem examination the spinal cord could be traced as a slender fibrous cord traversing the mass. (Case of Dr. Horace B. Davidson, Columbus, Ohio.)

under this heading. We have mentioned these tumors elsewhere. The dorsal tumors are usually dermoid cysts or teratomas. Giant cell tumor and ependymoma usually occur within the body of the sacrum. Ventral tumors are numerous and varied. Teratoma and chordoma are common in this region.

In this series there were 2 dorsal tumors, 1 an intraspinal dermoid cyst and the other an intraspinal teratoma. One occurred in the lower thoracic region, and the other in the upper lumbar region. Both tumors compressed the spinal cord, and both were associated with hairy moles on the skin surface. One patient was 3 years of age, and the other, 35.

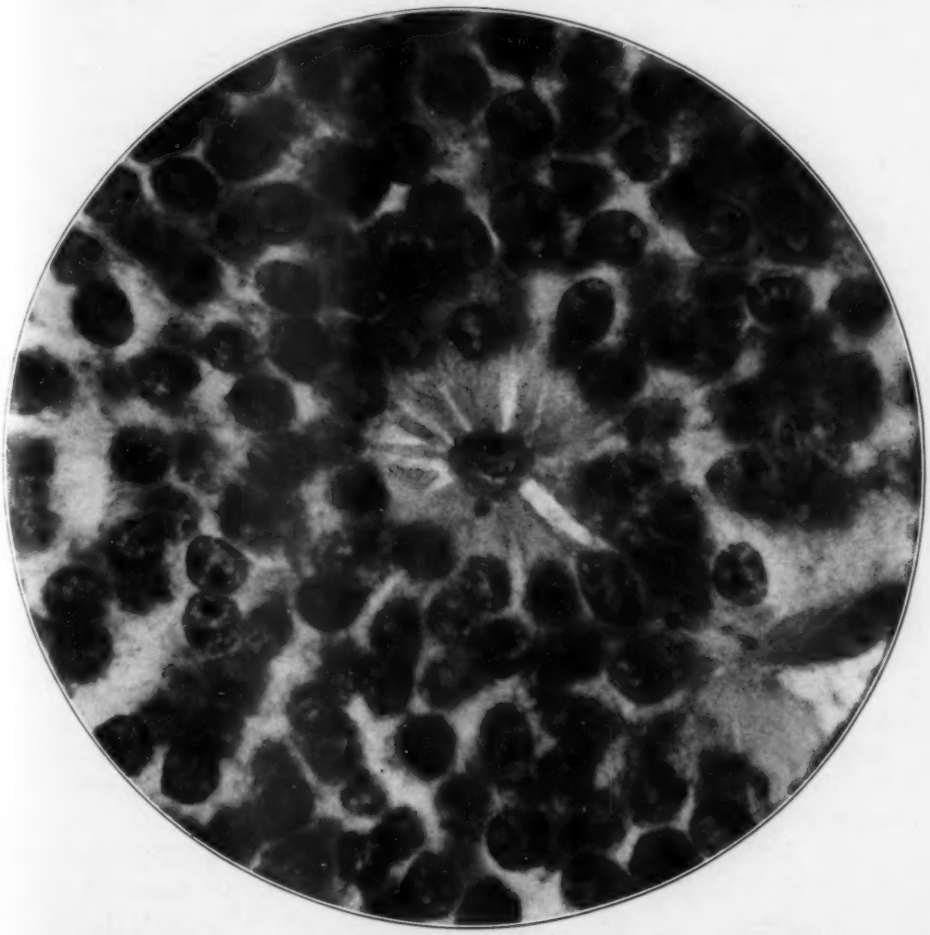

Fig. 38.—High power (oil immersion) photomicrograph of a neuroepithelioma, showing rosette formation, with well marked radiating cytoplasmic processes. (Case of Dr. Carleton B. Peirce, Ann Arbor, Mich.)

There were 3 ventral tumors in this series. One was a primitive neuroepithelioma, which has already been described with the glial tumors. The other 2 were teratomas in which all three of the primitive germ layers were present. Nerve tissue elements were present in both of these tumors. Both patients were infants, 1 of whom died soon after delivery and the other at 8 months of age.

DIFFERENTIAL DIAGNOSIS

Spinal tumor is frequently diagnosed as tuberculosis of the spine. It may be impossible to differentiate the one from the other by roentgen examination. This is true particularly in regard to the malignant tumors. Certain points, however, may be of use. Fray has pointed out that a vertebral body destroyed by malignant disease is apt to collapse uniformly, producing an "accordion effect." A triangular compression of a vertebral body is more common in tuberculosis. This variation in the type of collapse accounts for the fact that a gibbus is usually less marked in a neoplastic lesion than in a tuberculous lesion. A firm type of tumor, of course, may destroy a vertebral body and yet prevent any appreciable collapse. A characteristic of tuberculosis is destruction in the anterior portion of adjoining vertebral bodies, a very uncommon finding with spinal tumor. Compere and Garrison [34] stated that they have never seen tuberculosis primarily affect the neural arch or its appendages. These parts are frequent sites of neoplastic growth. Tuberculosis shows little tendency to regeneration of bone (Compere and Garrison), a marked feature with some tumors, especially after irradiation. A paravertebral shadow when it is not distinctive of some particular type of tumor is of no diagnostic value. The presence or absence of the intervertebral disk is likewise of little help. In some cases it may be found necessary to attempt an aspiration to obtain material for culture or for microscopic examination. In general, however, it may be said that in the absence of compression of the spinal cord, which is a symptom requiring operative relief, it is best to treat the doubtful condition by rest and by irradiation.

Pyogenic osteomyelitis of the spine should not, as a rule, be confused with neoplasm. The history of a preceding infection, the acute febrile state and the early destruction of the intervertebral disk should establish the diagnosis. Acute osteomyelitis of the spine is uncommon compared with tuberculosis.

The lesions of the spine which also must be borne in mind are those of typhoid fever, of syphilis, of fungous infection and of osteomalacia.

In any case of lesion of the spine in which the diagnosis is doubtful it is well to make a roentgen examination of the entire skeleton. The possibility of the presence of syphilis may be ruled out by serologic tests or by the response to specific therapy. The urine should be examined for Bence Jones bodies. The response to roentgen therapy may be helpful in the diagnosis.

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34. Compere, E. L., and Garrison, M.: Correlation of Pathologic and Roentgenologic Findings in Tuberculosis and Pyogenic Infections of the Vertebrae: Fate of the Intervertebral Disk, Ann. Surg. **104**:1038, 1936.

SUMMARY

Metastatic carcinoma, usually from the breast or from the prostate, is the most common neoplastic condition of the vertebral column. Cancer of the breast may involve any region of the spine; the lesions are usually multiple and destructive. Carcinoma of the prostate involves the sacrolumbar region and produces sclerosis of bone. These multiple lesions of the spine in adults must be differentiated from multiple myeloma, which produces multiple circular defects with a tendency to pathologic fracture and collapse. Involvement of the spine in Hodgkin's disease, lymphosarcoma and leukemia may simulate metastatic carcinoma.

Benign giant cell tumor and osteochondroma are the most common benign tumors of the spine. Giant cell tumor usually affects the spine of the young adult below the cervical region, tends to involve the neural arches and produces a trabeculated lesion outside the body of the vertebra. The healing phase of this condition produces bone cysts, which may also complicate Recklinghausen's disease associated with parathyroidism and demineralization of the entire spine. Osteochondroma may occur in any portion of the spine. The neural arches are affected by an osseous growth, with a clearly demarcated osseous shadow visible in the roentgenogram. Hemangioma of the vertebra is rare and produces characteristic vertical striations or well ordered radiating spicules of bone without collapse of the body of the vertebra.

Osteogenic sarcoma of the spine, including chondrosarcoma, osteolytic sarcoma and sclerosing sarcoma, may be secondary to multiple exostoses or to Paget's disease. These sarcomas show a wide age distribution. Chondrosarcoma of the spine tends to involve several vertebrae and produces characteristic calcified paravertebral shadows. The roentgenogram in a case of sclerosing sarcoma shows irregular formation of new bone in the soft parts. Osteolytic sarcoma is less characteristic in the roentgenogram and produces a rapidly extending region of osseous destruction, with infiltration of the soft parts. Chordoma affects either the spheno-occipital or the sacrococcygeal region of the spine of the adult and produces a bone-destructive lesion, which increases gradually over a period of months or years.

Twelve undifferentiated neuroblastic tumors—sympathicoblastomas—involved the spine in the present series. Such a tumor is usually situated in the lower part of the thoracic or in the lumbar region. It destroys bone and produces a paravertebral shadow. It tends to metastasize to the regional lymph nodes and to other bones and on microscopic examination is often mistaken for Ewing's sarcoma. Like Ewing's sarcoma it responds to irradiation. No typical Ewing sarcoma of the spine was found in the present series, and the tumors previously classed as such were thought on further study to be sympathicoblastomas.

A glial or nerve sheath tumor of the spinal cord may involve the vertebral column. A meningeal tumor usually affects the thoracic or the cervical region and may be visible in the roentgenogram, either because of erosion of bone or because of calcification in the tumor. Neurinoma or neurofibroma of a spinal nerve root more often causes erosion of bone than does a meningeal tumor. Neurinoma is most common in the lumbar and the sacral regions. This benign tumor attached to a nerve root may slowly erode bone, the pedicle, the laminas and the body of the vertebrae being affected in the order mentioned. Erosion is more rapid and more pronounced with a malignant nerve sheath tumor affecting the roots of the spinal nerves. Glial tumors producing changes in bone are rare. They are usually primitive neuroepitheliomas or ependymomas. In the sacrococcygeal region a benign or malignant teratoma may erode bone.

RIB REGENERATION FROM THE STANDPOINT OF THORACIC SURGERY

WARNER F. BOWERS, M.D.
MINNEAPOLIS

Factors concerning rib regeneration are of importance mainly to thoracic surgeons, but there are certain aspects which present more general interest. For example, data concerning the healing of fractures of the ribs may be applicable to fractures elsewhere. In some instances the surgeon finds regeneration of bone to be of advantage, as in the Semb [1] type of extrafascial apicolysis, in which new bone formation aids in maintaining collapse of the lung. Knowledge of the effect of removal of periosteum on the stability of the chest wall in such procedures as unroofing for chronic empyema cavities is also important. On the other hand, there is a definite group of situations in which rib regeneration is a distinct disadvantage. For example, in the surgical treatment of pulmonary tuberculosis some untoward reaction, such as traumatic infection or the spread of tuberculosis to the opposite lung, may cause the postponement of subsequent stages of the procedure until rib regeneration has made collapse less effective than it might have been. Also, in the treatment of empyema thoracis and abscess of the lung, regeneration may be a disadvantage because drainage is interfered with before the underlying cavity has closed. Lastly, in empyema, Hart [2] and Foster [3] concluded that osteomyelitis may develop in a rib regenerating in an infected field and that the new rib may thus be a cause of chronic disease.

REVIEW OF THE LITERATURE

THEORIES OF OSSEOUS REPAIR

There are three main schools of thought with reference to osteogenesis and repair of bone.

From the Department of Surgery of the University of Minnesota School of Medicine.

A thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Semb, C.: Personal communication to the author.

2. Hart, D.: Empyema: Treatment by Tidal Irrigation and Suction, Arch. Surg. **19**:1732-1765 (Dec.) 1929.

3. Foster, L. C.: Treatment of Acute Empyema Thoracis, Ann. Surg. **92**: 212-221, 1930.

Periosteal Regeneration.—According to Duhamel,[4] Syme,[5] Ollier,[6] Axhausen,[7] Haas,[8] Mayer and Wehner,[9] Phemister,[10] Berg and Thalhimer,[11] Rohde,[12] Blaisdell and Cowan,[13] Mock,[14] Ham,[15] Smith,[16] Haldeman,[17] Leadbetter,[18] Riess,[19] Schepelmann,[20] Bisgard [21] and many others, periosteum and endosteum are definite organs for the formation and repair of bone. Osteoblasts, according to this theory, never come from adult bone cells, but arise from the cells of the periosteum and, to a lesser extent, from the endosteum.

Osteoblastic Regeneration. — Goodsir,[22] Macewen,[23] Brown and Brown,[24] Moore and Corbett,[25] Davis and Hunnicutt,[26] Gallie and

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(Footnotes continued on next page)

Robertson,[27] Cohn and Mann,[28] Ely,[29] Keith,[30] Sever,[31] Jaffe[32] and others have stated that periosteum serves simply as a limiting membrane and a convenient source of blood supply, but plays no active role in osteogenesis. These physicians have upheld one of the two following opinions: (1) After injury bone cells are liberated from their lacunas, and these multiply to form new bone; (2) after injury wandering connective tissue cells are drawn to the site of reaction and through their pluripotentiality become osteoblasts.

Extracellular Deposition of Calcium Salts.—This theory, advocated by Bancroft,[33] Leriche and Policard,[34] Asami and Dock,[35] Neuhof,[36] Huggins,[37] Roome and McMaster,[38] Petrow,[39] Murray[40] and others, stated that there is no definite bone-producing cell but that after injury calcium salts are laid down in the framework of the adjacent connective tissue by chemotaxis. These connective tissue cells then become bone cells by metaplasia, or by functional adaptation.

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30. Keith, A.: Growth and Regeneration of Bone, Brit. J. Surg. **5**:685-693, 1918; **6**:19-23 and 160-165, 1918.

31. Sever, J. W.: Nonunion in Fracture of the Shaft of the Humerus, J. A. M. A. **104**:382-386 (Feb. 2) 1935.

32. Jaffe, H. L.: Structure of Bone: Wolff's Law, Arch. Surg. **19**:24-52 (July) 1929.

33. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. **5**:646-677 (Nov.) 1922.

34. Leriche, R., and Policard, A.: Le périoste et son rôle dans la formation de l'os, Presse méd. **26**:143, 1918.

35. Asami, G., and Dock, W.: Experimental Studies on Heteroplastic Bone Formation, J. Exper. Med. **32**:745-666, 1920.

36. Neuhof, H.: Fascial Transplantation into Visceral Defects, Surg., Gynec. & Obst. **24**:383-427, 1917.

37. Huggins, C. B.; McCarroll, H. R., and Blocksom, B. H.: Experiments on the Theory of Osteogenesis; Influence of Local Calcium Deposits on Ossification; Osteogenic Stimulus of Epithelium, Arch. Surg. **32**:915-931 (June) 1936.

38. Roome, N. W., and McMaster, P. E.: Influence of Venous Stasis on Heterotopic Formation of Bone, Arch. Surg. **29**:54-58 (July) 1934.

39. Petrow, N. N.: Zur Frage nach der Quelle der Regeneration bei Knochenüberpflanzung, Arch. f. klin. Chir. **105**:915-923, 1914.

40. Murray, C. R.: Repair of Fractures, Minnesota Med. **13**:137-152, 1930.

TRANSPLANTATION OF BONE

Investigators have differed in their opinions concerning the fate of autoplastic bone grafts, according to the theory of osteogenesis they have supported. Those who have concluded that bone in itself is osteogenic have interpreted their results to show that bone grafts grow; those who have concluded that periosteum is the source of new bone have stated that bone grafts die and are absorbed or may act as a framework for new bone, and those who have been convinced that connective tissue forms new bone have stated that the graft acts as a source of calcium salts, which stimulates metaplasia in the connective tissue.

Macewen was able to show phenomenal results in his experiments. Free grafts of bone grew, chips of bone produced new bone and chips implanted into muscle tissue produced large plaques of new bone. Phemister, Haas,[41] Axhausen, Thalhimer and Brooks [42] have published work which seems to show that free transplants of bone act as a source of regeneration and are not merely a trellis into which new bone grows from neighboring sources.

McWilliams,[43] Phemister, Rohde, Ham, Pollack [44] and others have adopted the very reasonable view that the success or failure of a graft of bone or periosteum, or both, depends on the rapidity with which the graft is able to establish a new and adequate blood supply. According to this view, small bone grafts do not need a periosteal covering because they easily become vascularized, whereas larger grafts may fail because of a lack of this vascularity. Periosteum on these larger grafts may insure success because of the preformed vascular channels present.

Brooks and Hudson, using dogs, obtained success with 84 per cent of autoplastic grafts of the ulna, as compared with success with 76 per cent of homoplastic grafts in the same region. They concluded that the compatibility of tissues is an important factor in the success of these grafts. They used intravital staining to demonstrate the formation of new bone.

Camitz, Holmgren and Johansson [45] were successful with homologous transplants in dogs and found that all elements of the graft were concerned in healing and in the regeneration of bone.

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41. Haas, S. L.: Regeneration of Bone and Cartilage at the Costochondral Junction, Surg., Gynec. & Obst. **19**:604-617, 1914.

42. Brooks, B., and Hudson, W. A.: Studies on Bone Transplantation, Arch. Surg. **1**:284-309 (Sept.) 1920.

43. McWilliams, C. A.: Periosteum in Bone Transplantation, Surg., Gynec. & Obst. **18**:159-169, 1914.

44. Pollack, W. E.; McKenney, P. W., and Blaisdell, F. E.: Viability of Transplanted Bone, Arch. Surg. **18**:607-623 (Feb.) 1929.

45. Camitz, H.; Holmgren, H., and Johansson, H.: Study of Bone Transplants, Acta chir. Scandinav. **75**:1-67, 1934.

Gill [46] showed that autogenous transplantation of entire metatarsal bones in a dog's paws was accompanied by moderate success. He also cited many clinical instances (Lexer) of homoplastic transplantation of fingers, toes, half joints and even, in a few instances, entire knee joints.

REGENERATION OF BONE

Ely,[47] in studying the healing of fractures in cats, became convinced that the periosteum served only as a container for the reparative callus, acting also in the capacity of a splint. Gallie and Robertson also stated that periosteum has no osteogenic function, serving merely as a convenient source of blood supply. Macewen expressed the opinion that periosteum by pressure on the osteoblastic mass serves to limit the amount of callus formed.

On the other hand, Haldeman found periosteum to be the chief factor in the healing of fractures. He stated that endosteal callus aids, but that in the absence of periosteum it is often incapable of causing, complete union. He found that the interposition of periosteum between the fractural fragments caused nonunion, because new bone did not tend to bridge the defect in the absence of periosteum.

Various investigators have obtained new bone formation after subcutaneous injection of emulsions of periosteal cells. Carrel [48] and others have found that periosteum retains its osteogenic properties even after having been placed in cold storage for several days before implantation. Recently, Bisgard [49] has implanted periosteal and osseous grafts into the anterior chamber of the eye of the rabbit, with and without the addition of calcium salts. This is essentially a tissue culture method, and he found that both types of graft are osteogenic. The addition of bone ash or bone salts made no change in the results, nor would the fascia ossify even in the presence of ash or bone salts.

HETEROTOPIC FORMATION OF BONE

It has been known for a long time that true bone may form in healing epigastric wounds, in occluded ureters and renal pelves and in fascial grafts used in repairing defects in the urinary bladder. Keith [50]

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46. Gill, A. B.: Transplantation of Entire Bones and Their Joint Surfaces, Ann. Surg. **61**:658-671, 1915.

47. Ely, L. W.: Experimental Study in Healing of Fractures, Arch. Surg. **5**:527-560 (Nov.) 1922.

48. Carrel, A.: Preservation of Tissue and Its Applications in Surgery, J. A. M. A. **59**:523-527 (Aug. 17) 1912.

49. Bisgard, J. D.: Ossification: Influence of the Mineral Constituents of Bone, Arch. Surg. **33**:926-939 (Dec.) 1936.

50. Keith, A.: Origin and Nature of Osteoblasts, Proc. Roy. Soc. Med. **21**: 301-308, 1927.

discussed these observations and felt that the phenomena could be explained only by the hypothesis of Leriche, that bone is formed in the presence of reacting connective tissue and of excess calcium salts. Asami and Dock had previously studied heterotopic formation of bone in the urinary tract, stating that new bone is formed by metaplasia of fixed connective tissue cells. Neuhof, in his extensive work with fascial transplants, found that there was early disintegration followed by replacement with firm fibrous tissue. Bone frequently was formed, especially in the bladder. He also explained this osteogenesis on the basis of metaplasia in the connective tissue. Huggins [51] concurred in the observations of the effect on the formation of bone when bladder mucosa was transplanted into connective tissue. He found that bladder mucosa normally secretes calcium and phosphorus, and he indorsed the theory of Leriche. Roome and McMaster [38] found that venous stasis favored the laying down of heterotopic bone. They further observed that this new bone tended to be absorbed subsequently. This coincides with the theory of Wolff [52] which stated that bone is anatomically adapted to its function, and with the idea of Roux,[53] which is that functionless bone is absorbed.

CHEMICAL INHIBITION OF RIB REGENERATION

Head,[54] in 1927, was the first to advocate the use of chemical inhibition of rib regeneration in thoracic surgery as an aid to collapse, exposure and drainage. In an experimental series he used a stick of silver nitrate, a 50 per cent solution of silver nitrate, concentrated chromic acid and Zenker's solution. He found that silver nitrate gave extensive necrosis with a high incidence of pleural perforation and death. Chromic acid gave satisfactory inhibition of regeneration for four weeks, and Zenker's solution, for six weeks. It is interesting to note that Head stated that chemical inhibition of rib regeneration is contraindicated in cases of extrapleural thoracoplasty for surgical collapse in pulmonary tuberculosis. He based this statement on the assumption that since the mediastinum is not fixed, permanent mobilization of the chest wall would produce paradoxic respiration in the collapsed lung, with a consequent reduction in the already compromised vital capacity.

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51. Huggins, C. B.: Formation of Bone Under the Influence of Epithelium of the Urinary Tract, Arch. Surg. **22**:377-408 (March) 1931.

52. Wolff, J.: Das Gesetz der Transformation der Knochen, Berlin, A. Hirschwald, 1892.

53. Roux, W.: Die Entwickelungsmechanik, ein neuer Zweig der biologischen Wissenschaft, in Vorträge und Aufsätze über Entwickelungsmechanik, Leipzig, Wilhelm Engelmann, 1905, vol. 1, pp. 1-283.

54. Head, J. R.: Prevention of Regeneration of the Ribs, Arch. Surg. **14**:1209-1215 (June) 1927.

Meiss [55] in 1930 noticed that regeneration of the ribs hindered collapse in successive stages of thoracoplasty. In dogs, he resected ribs and applied Dakin's solution of formaldehyde U. S. P. diluted 1:10, chromic acid and Zenker's solution to the periosteal beds. Solution of formaldehyde was found to give inhibition of regeneration for at least three months and was superior to the other agents used because it did not cause pleural perforations. Meiss advocated the application of solution of formaldehyde to the periosteal beds after rib resection to facilitate the later stages of thoracoplasty, to allow longer periods between stages and to facilitate an intrathoracic operation if one is needed subsequently.

In 1930 Torraca [56] treated the periosteal beds with thermocautery, phenol, solution of formaldehyde, Bouin's solution, alcohol and silver nitrate. All of these except silver nitrate gave inhibition of regeneration, but the application of most of them was accompanied by perforation and death. Solution of formaldehyde was found to be the most satisfactory and gave the lowest incidence of pleuropulmonary adhesions. Zenker's solution has been successfully used by Trout [57] for inhibition of rib regeneration in thoracoplasties.

The first report of the extensive clinical use of the chemical inhibition of rib regeneration is that of Van Allen [58] in 1933. He stated that this procedure could be used to advantage not only in thoracoplasties but in graded operations for chronic empyema and bronchiectasis, in cardiolysis to insure permanent pliability of the precordium and in rib resections for acute empyema, abscess of the lung or cautery pneumonectomy. Van Allen [58] reported 40 cases of various types and could see no disadvantage in the use of solution of formaldehyde (U. S. P., diluted 1 to 10). He found that Zenker's solution gave inhibition for a shorter period and allowed fragmentary regeneration.

In the following year, Jachia [59] reported good results from the use of Zenker's solution for inhibition in cases requiring multiple stage thoracoplasty.

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55. Meiss, W.: Experimenteller Beitrag zur Vereinfachung der Thorakoplastik in mehreren Tempi, Zentralbl. f. Chir. **57**:349-354, 1930.

56. Torraca, L.: Ricerche sperimentali sui mezzi apti ad impedire la regenerazione ossea dopo l'asportazione sottoperiostea delle costole, Clin. chir. **6**:1433-1452, 1930.

57. Trout, H.: Release of Pericardial Adhesions, Arch. Surg. **23**:966-995 (Dec.) 1931.

58. Van Allen, C. M.: Chemical Treatment of Periosteum in Thoracoplasty to Inhibit Rib Regeneration, Ann. Surg. **97**:368-373, 1933.

59. Jachia, A.: Chemical Destruction of Periosteum in Treatment of Chronic Empyema, J. Thoracic Surg. **3**:623-633, 1934.

Haight [60] in 1936 stated that as a matter of routine he applies solution of formaldehyde U. S. P. diluted 1 to 10 to the periosteal beds and is thereby able to lengthen the interval between the stages of thoracoplasty. He concluded that collapse is improved and subsequent stages are facilitated.

RIBS OVERLYING EMPYEMA CAVITIES

Bisgard [61] in 1933 called attention to the fact that the external form of ribs overlying empyema cavities is changed, and that there is new bone formation along the inferior and internal aspect of these ribs. He noted this change even in acute empyema and concluded that these changes could be utilized as a means of estimating the size of empyema cavities by roentgenograms. He explained this proliferation of bone on the assumption that the infected pleura causes periostitis, which stimulates osteogenesis, and stated that the successive layers of new bone indicate a series of such stimuli. Bisgard [61] invoked Wolff's law of functional adaptation to explain the change in contour of the ribs, believing that the centripetal pull of the contracting pleural scar was the force modifying costal architecture.

PROBLEM AND PURPOSE OF THE STUDY

The process of normal osteogenesis is not known, and the sequence of events in osseous regeneration is poorly understood. The literature on these two problems is voluminous and conflicting even in the fundamental concepts. However, Ham's histologic studies of the early phases of the regeneration of bone may be accepted as reflecting the usually adopted beliefs. Ham [15] found that after fracture of the rabbit's rib the adult bone cells died for a distance of 1 to 5 mm. Fragments of bone died also, and this is contrary to the view of Macewen, who said that fragments become centers of osteogenesis. Ham found the lacunas empty or containing pyknotic nuclei. Beyond this area the adult bone cells showed no evidence of proliferation. These observations were borne out by those of Blaisdell and Cowan, Berg and Thalhimer, Mayer and Wehner, Rohde and Mallory. Ham noted that the periosteal osteoblasts after fracture showed mitosis and that gross examination of the periosteum showed it to be thicker and more cellular. The external layers of cells were rapidly dividing, whereas the deeper layers were laying down a cartilaginous matrix. These layers were solid masses of differentiating cells, without blood vessels. Somewhat deeper, new bone formation was found, and here vascularity was noted. Ham pos-

60. Haight, C.: Complementary Anterior Thoracoplasty for Pulmonary Tuberculosis, J. Thoracic Surg. **5**:453-470, 1936.

61. Bisgard, J. D.: Ribs Overlying Empyema Cavities, Arch. Surg. **27**:941-959 (Nov.) 1933.

tulated that the presence of local deposits of calcium salts and a good blood supply are necessary in the metamorphosis of osteogenic cells into bone. He stated, further, that cartilage results from the growth of osteogenic cells in the absence of these factors.

Much of the controversy in the literature hinges on questions of definition and of whether or not the removed periosteum carries with it tiny spicules of bone which may be responsible for subsequent new bone formation. Those who claim that denuded adult bone has osteogenic powers are accused of allowing clumps of cells from the cambium layer of the periosteum to remain on the surface of the graft. That the stripped periosteum does not usually carry spicules of bone with it has been shown by Bisgard,[62] but such questions do not lend themselves well to absolute proof. The thoracic surgeon is only casually concerned in such academic discussions, but he is definitely interested in knowing what he may expect from periosteum and from denuded ribs as seen in the various types of operative procedures. With this idea in mind, an attempt has been made to determine the fate of periosteum, ribs devoid of periosteum and periostealized ribs devoid of blood supply in such procedures as rib resections, thoracoplasties and pneumolyses. Free grafts of bone and periosteum have been studied, and methods of chemical inhibition of rib regeneration have been investigated.

There have been numerous definitions of periosteum, some going so far as to state that periosteum is not an anatomic structure but is rather a region of potential physiologic activity. For purposes of clarity let it be understood that when periosteum is mentioned in this paper that fibrous membrane which is readily stripped from bone by blunt dissection is meant. Its various layers and components will not be considered.

By definition, an osteoblast is a primitive cell which has the ability to develop into osseous tissue. Practically, this definition is not helpful, because it is not histologically possible to differentiate osteoblasts from fibroblasts. For this reason, physicians' knowledge of osteoblasts is largely theoretic, and what they really study microscopically are osteophytes. According to one view, osteoblasts and fibroblasts are identical, but were this true new bone should develop from new connective tissue in the absence of periosteum. On the contrary, as will be shown subsequently, these fibroblasts do not lay down new bone even when they develop in an osseous defect.

MATERIAL AND METHODS

In the experimental part of this investigation dogs were used exclusively. The animals were not selected, and their exact ages are unknown. In general, however, it may be said that, judging from the teeth and from the readiness with which

62. Bisgard, J. D.: Osteogenesis, Arch. Surg. **30**:748-776 (May) 1935.

the periosteum could be stripped from the ribs, the dogs were young. A few old dogs were used in order to determine the effect of the age factor on the regeneration of bone. All operations were performed with the dogs under pentobarbital sodium anesthesia, 35 mg. per kilogram of body weight being administered intraperitoneally in aqueous solution. The operative site was shaved and prepared with iodine and alcohol. Strict aseptic precautions were used in all operations. In some instances a long oblique muscle-splitting incision was used to expose several ribs, while in others individual incisions were made over each rib which was to be attacked. In the thoracoplasties and similar operations adjacent ribs were used, but in all other experiments alternate ribs were left intact. In many of the dogs three alternate ribs on the right and three on the left were attacked. Linen and silk were used as suture material. When gross infection followed the operation the dog was not included in the series. Roentgenograms of the thorax were taken before the operation, immediately after the operation and at intervals during the period of observation. The dogs were killed at intervals varying from four weeks to four months, and the specimens were then obtained, with several normal ribs on each side for purposes of control. In most instances the specimens were described grossly, roentgenograms were then made and in some cases photographs of the dried specimens were taken. Usually, however, after the roentgenograms were taken the specimens were fixed in solution of formaldehyde, decalcified and sectioned. Decalcification was accomplished with (1) 5 per cent nitric acid, (2) 10 per cent nitric acid and 80 per cent alcohol in equal parts and (3) 5 per cent hydrochloric acid. The latter solution was found to be preferable because the tissues could be cut with greater ease and because the xanthoprotein formed by nitric acid seemed to interfere with staining reactions. All sections were stained with hematoxylin and eosin. Dogs dying within one month were included only if the specimens could be obtained before postmortem autolysis had developed. These early specimens were not used in computing the final results but were included simply to throw some light on the early processes of regeneration of bone.

Several attempts were made to use intravital staining of new bone by the intraperitoneal injection of 10 cc. of a saturated aqueous solution of sodium alizarin sulfonate twice weekly, but in no instance was the attempt successful.

The clinical data are based on patients from the University Hospital, who had empyema thoracis or pulmonary tuberculosis requiring surgical collapse. The specimens were prepared in the same manner as those from the experimental animals.

EXPERIMENTAL DATA

ROLE OF PERIOSTEUM IN RIB REGENERATION

Subperiosteal Rib Resection.—In 15 dogs, a 3 cm. segment of rib was excised subperiosteally. The remaining periosteal bed was not sutured into tubular form but was left as a flat strip. Specimens were obtained after eight, ten, fourteen, thirty and ninety days. The 2 eight and ten day specimens showed organizing hemorrhage in the periosteal bed, and in 1 there was very early evidence of new osseous formation. The 2 specimens obtained after fourteen days showed early regeneration of bone. In 8 of the 10 specimens obtained after one month complete regeneration had taken place, while in the other 2 there was a small central area not yet filled by new bone. The three month specimen was firmly regenerated, and on section the new bone was seen to have a normal adult type of architecture.

The microscopic sections showed new bone forming from connective tissue. In 20 per cent of the one month specimens cartilage had been formed and was

undergoing ossification, in addition to the new bone which was being formed from connective tissue (fig. 1).

Rib Resection with Removal of Periosteum.—In 15 dogs a 3 cm. segment of rib was excised, all of the periosteum being removed with it. This left only the endothoracic fascia to protect the pleura from perforation. Four of the dogs died of perforation and pneumothorax in eight, ten and fourteen days. In 1 dog, when it was killed after one month the lung was adherent to the parietal pleura under the operative site. There was no essential difference in the early and the late specimens in these experiments except in the maturity of the fibrous tissue. In no instance was new bone laid down in an attempt to bridge the defect. The ends of the rib all were smoothly rounded off and were covered by fibrous tissue. In 30 per cent of the specimens there were spurs of new bone where the rib had been excised, the periosteum apparently having been elevated somewhat from the bone by operative trauma (fig. 2).

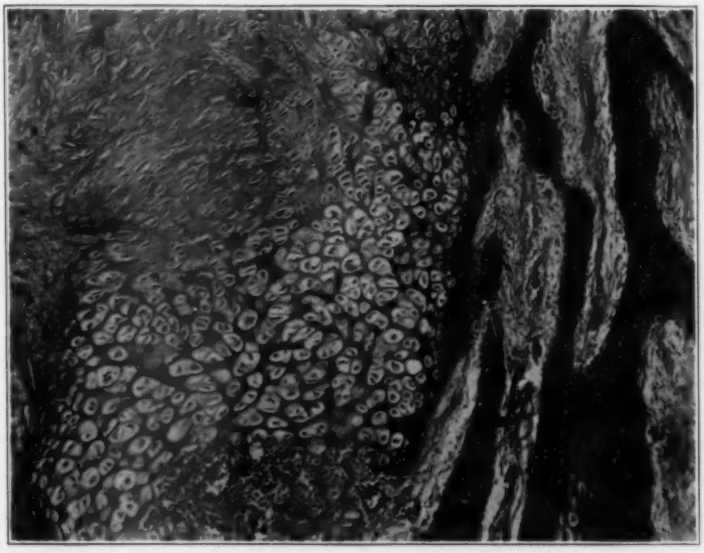

Fig. 1.—This photomicrograph shows the regeneration of new bone in the periosteal bed one month after the subperiosteal resection of a segment of rib. The transition from cartilage to bone is well shown and the change from connective tissue to bone is also illustrated.

Interposition of a Flap of Muscle Between the Rib and Its Periosteum.—In 15 dogs a rib was separated from its periosteum for a distance of 3 cm. A viable flap of muscle was fashioned and interposed between the rib and its periosteum, as described by Alexander.[63] The flap was then sutured so as to maintain this relationship. None of the dogs died of this operation, and there were no adhesions beneath the site when the dogs were killed. Specimens were obtained in eight, ten, fourteen, thirty and ninety days. In the early specimens there were no changes in the denuded rib, and no new bone had been laid down. Of the one month

63. Alexander, J.: Supraperiosteal and Subcostal Pneumolysis with Filling of Pectoral Muscles, Arch. Surg. **28**:538 (March) 1934.

specimens, 80 per cent showed new bone being formed in the periosteum which had been separated from the rib by a muscle flap. In 60 per cent there was an incomplete bridge of new bone, and in 20 per cent the bridge had formed a complete new rib. Six of the denuded ribs were being absorbed. They were irregularly roughened, and the roentgenogram demonstrated them to be atrophic. Microscopically, when sectioned, some of them were seen to be disintegrating and to be surrounded by a dense layer of fibrous tissue (fig. 3). The three month specimen had a well developed new periosteal rib which showed an adult type of arrangement of the bone cells. The old rib was dead, and fragmentation had set in.

In 3 other dogs a flap of muscle was interposed between the rib and the periosteum in two adjacent ribs. After six weeks each of these specimens showed an incomplete bridge of periosteal new bone, and the denuded ribs were atrophic and smaller in diameter than they had been before (figs. 4 and 5).

Fig. 2.—This photomicrograph shows the dense bed of fibrous tissue formed one month after a segment of rib had been removed with its periosteum. There is no new bone formation.

Insertion of a Foreign Body Pack Between a Rib and Its Periosteum.—In 2 dogs the periosteum was separated from five adjacent ribs, and half of a celluloid soap dish was inserted between the ribs and the periosteum, the concavity being turned toward the ribs. These specimens were removed after six weeks. In 1 dog there were pleuropulmonary adhesions beneath the operative site. In both specimens the ribs were irregularly absorbed and were atrophic. The periosteal beds showed varying degrees of regeneration, from spurs of bone at the angles of reflection to complete solid bridges of new bone (fig. 6). This same procedure was repeated in 2 instances, a sterile gauze pack being substituted for the celluloid device and a molded mass of paraffin being used in 1 instance between the ribs and the periosteum. The specimens in which the gauze pack had been used were recovered after six weeks. In both the ribs were being absorbed and were covered by a

layer of granulation tissue. All of the periosteal beds showed new osseous formation from connective tissue (fig. 7). The specimen in which the paraffin pack had been used was obtained after three weeks, and the changes noted were identical with those previously described.

Multiple Subperiosteal Resection of Ribs.—In 5 dogs modified thoracoplasties were done. In 4 dogs five ribs were resected, and in the other, in two stages, at weekly intervals, nine ribs were removed. The excised segments extended from the costochondral junction to within 2 cm. of the transverse spinal processes. No external compression was employed. The specimens were recovered one, two and three months after the final stage. In every case paradoxic respiratory motion was noticed for about two weeks after the operation. In two of the experiments old dogs were used, and in 1 after one month and in the other after three months scant new bone formation could be demonstrated. In 1 specimen after one

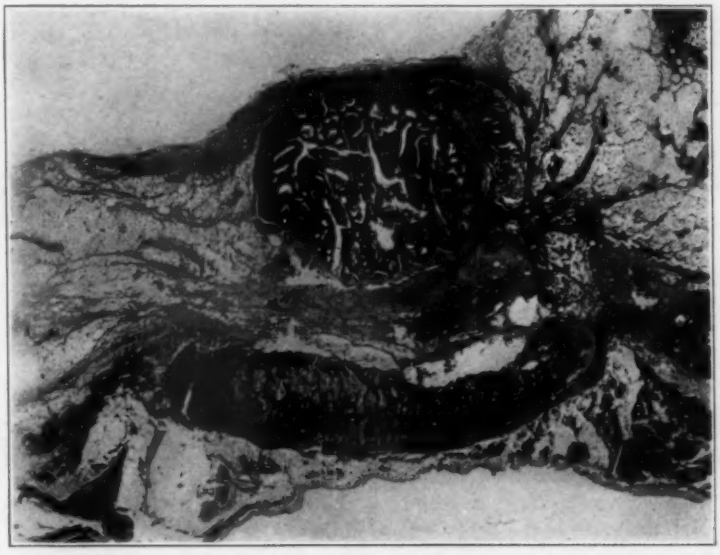

Fig. 3.—This photomicrograph clearly demonstrates the fact that periosteum is capable of new osseous formation. The rib was separated from its periosteum, and a muscle flap was interposed. This shows the result after one month. The old rib shows some irregular erosion of its surface. The new bone in the periosteal bed does not have the contour of adult rib, but in the longer experiments the new rib became more rounded and assumed an adult type of architecture.

month there was firm regeneration in a position of good collapse, while in another there was incomplete regeneration and slight collapse. The two stage, nine rib specimen was removed after two months. It was found that there was very little collapse, owing to the rapid regeneration of the ribs removed at the first stage of the procedure. Some fractures of this new bone were seen. The ribs removed at the second stage were as yet but partially regenerated. In only 1 instance was new bone being formed from ossifying cartilage. In all of the other specimens, the new bone could be seen to be originating from the connective tissue.

Chemical Osteomyelitis of Ribs.—In 5 dogs a small drill hole was made in a rib and 1 minim (0.06 cc.) of croton oil was injected into the marrow cavity.

The specimens were recovered after four, eight, fourteen, thirty and forty-two days. After four days there were no gross changes, but microscopically there was a marked increase in the cellularity of the periosteal layer. The eight day specimen was not sectioned, because an extensive subcutaneous abscess developed, and the rib was denuded of its periosteum for 3 cm. on each side of the drill hole. After two weeks there was a moderate amount of new bone around the drill

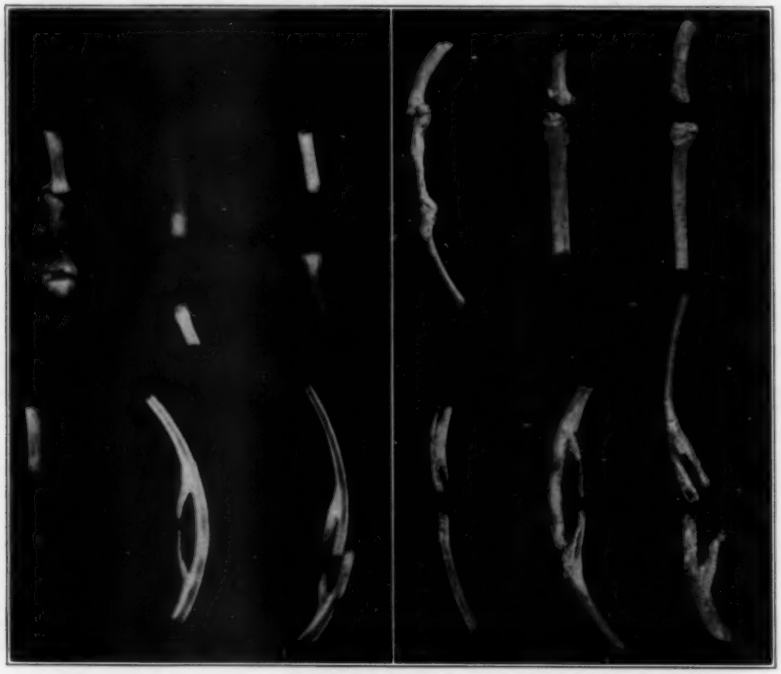

Fig. 4.—The roentgenogram at the left shows the progress of osseous regeneration after one month. In the upper left hand corner, regeneration after subperiosteal resection is seen to be almost complete. Note that regeneration is not originating from the ends of the ribs. In the specimen to the right, the periosteum was removed with the rib segment. Observe the absence of osseous regeneration and the eburnation of the rib ends. The specimen at the top on the right shows the inhibitory effect of the application of Zenker's solution to the periosteal bed. There is a small spur of new bone from the periosteum, with eburnation of the rib end. The periosteal bed of the specimen on the lower left was treated with solution of formaldehyde U. S. P. diluted to 1 to 10. Note the absence of new bone and the more nearly normal appearance of the remaining bone. To the right of it is seen the result of the interposition of a muscle flap between the rib and its periosteum. The bridge of new bone is not quite complete, and there is no atrophy, but some increased density, of the old rib. In the specimen at the bottom on the right is seen the result of fracture when the periosteum is separated from the fragments by a muscle flap. The rib ends are irregularly eroded, and there has been no attempt at healing. The periosteal bridge, again, is incomplete. The figure at the right is a photograph of the same specimens after the drying and removal of the soft tissue. All of these specimens are from the same dog and represent alternate ribs, three on the right and three on the left.

Fig. 5.—This roentgenogram shows the reparative changes after three months. At the upper left, after subperiosteal resection, regeneration is complete and there has been a fracture of the new bone, probably due to respiratory excursion. Note that an adult type of architecture is shown in the new bone. To the right is seen the specimen in which periosteum was removed with the rib segment. There is no regeneration. On the upper right is seen the result of the application of Zenker's solution to the periosteal bed after a subperiosteal rib resection. The lower left hand specimen shows the inhibitory effect of solution of formaldehyde on the periosteal bed. The next specimen shows a periosteal bridge of new bone, formed when the rib was separated from its periosteum by a muscle flap. In the specimen at the lower right there has been no attempt at repair of the fracture when the periosteum was separated from the fragments by a muscle flap. The rib fragments are eburnated and irregularly absorbed.

Fig. 6.—This photograph shows the result of an experiment in which, six weeks previously, the periosteum was separated from a 6 cm. area on five adjacent ribs and a celluloid device was inserted between the ribs and their periosteum. This rib clearly shows the firm and extensive formation of new bone from the periosteum. The original rib is seen to be atrophic and partially absorbed.

hole. This new bone almost completely surrounded the rib and apparently arose from the periosteum, blending into the surrounding fibrous tissue. After one month there was a large amount of new bone, apparently arising in a similar manner. The six week specimen showed a moderate amount of new bone, which now had taken on an adult type of architecture.

ROLE OF PERIOSTEUM IN THE HEALING OF COSTAL FRACTURES

Separation of the Periosteum from the Site of the Fracture by a Flap of Muscle.—In 15 dogs a rib was exposed and the periosteum was incised for a

Fig. 7.—This roentgenogram shows the result six weeks after the insertion of a sterile gauze pack between the periosteum and the ribs. Periosteal new bone is well shown, and there is marked atrophy of the deperiostealized ribs.

distance of 3 cm. The periosteum was then bluntly separated from the rib and a flap of viable muscle was interposed between the rib and its periosteum. Care was taken to jeopardize the blood supply as little as possible, and the trauma was minimal. After the flap of muscle had been sutured in place, a simple clean fracture of the denuded rib was accomplished over the center of the flap by means of the rib shears. The effect of this procedure, then, was to produce a fracture of the rib, the fragments being devoid of periosteum for 1.5 cm. on each side of the fracture. One specimen was obtained after eight days, 1 after ten days, 2 after fourteen days, 10 after thirty days and 1 after ninety days. In the specimens

obtained within one month there were no gross evidences of new bone formation. The periosteum in 2 specimens, however, showed new bone in an early stage when sectioned. In 1 instance a fragment of rib punctured the pleura, and the dog died of pneumothorax. In 1 instance the lung was adherent to the pleura under the operative site. From one of the fragments a mass of endosteal granulation tissue was protruding.

In one month specimens there was no evidence of new bone formation from the fragments devoid of periosteum. In every instance the fragments were more or less firmly bound together by dense fibrous tissue. In most of the specimens the ends of the fragments were of smaller diameter than the remainder of the rib, and on roentgenoscopic examination they were seen to be eburnated. Microscopic section showed the lacunas to be empty, and there was evidence of absorption. In the periosteum, separated from the fragments by the muscle graft, 7 of the 10 specimens showed new bone formation. In some instances the new bone was represented by spurs at the angles of reflection of the periosteum from the bone, while in others there was an incomplete bridge of new bone. In the specimen removed after three months there was a heavy and complete periosteal bridge of new bone. There was dense fibrous union of the fragments, which were becoming absorbed.

IMPORTANCE OF THE PERIOSTEAL BLOOD VESSELS IN REGENERATION OF BONE

Destruction of the Blood Supply from the Intercostal Bundles.—In 19 dogs the intercostal bundles were carefully dissected from two to six adjacent ribs, the periosteum being left intact on the ribs. In this manner all blood supply to the perisoteum from the intercostal bundles was destroyed. In 5 dogs these intercostal bundles were allowed to fall back into their normal positions, while in the other 14 the bundles were separated from the ribs by a celluloid device or by a gauze pack. Specimens were studied after six weeks. In the dogs which died early the periosteum was found to be necrotic and to have sloughed from the ribs in irregular patches. In the 5 dogs in which the intercostal bundles had been allowed to fall back into position the periosteum had been able partially to revascularize itself, but in each instance there was found definite atrophy of bone on roentgen examination. In those in which foreign bodies had been interposed between the ribs and the intercostal bundles the degree of rib absorption varied markedly. In some dogs, the roentgen study showed simply surface roughening and rarefaction. In others there was definite absorption, with spurs of new bone at the edges. Occasional nodules of new bone had formed from the haversian canals. In 2 instances all of the ribs in the operative area had undergone complete solution of their continuity and there was a draining sinus through the wound from which bony spicules were being extruded (fig. 8). In all of the specimens the ribs which were being absorbed were covered by heavy layers of granulation tissue. In 1 specimen the filaments of granulation tissue measured 8 to 10 cm. in length. The gauze pack had eroded the pleura, and these filaments were protruding into the pleural cavity. The remainder of the pleura under the area of the pack was thickened.

SPECIFICITY OF FREE PERIOSTEAL GRAFTS

Abdominal Subfascial Implants of Rib Periosteum.—In 7 dogs a 2 cm. segment of rib was excised with its periosteum. The periosteum was then bluntly stripped from this fragment and, free from bone spicules, so far as gross examination

could determine, was implanted into the abdominal wall just beneath the anterior sheath of the rectus abdominis muscle. Hemostasis was adequate. One dog died from some other cause on the ninth day. Specimens were recovered from the other animals after six weeks. The nine day specimen showed no evidences of new bone formation on gross examination, in the roentgenogram or on section. There was a dense inflammatory reaction at the site of implantation. The 6 specimens recovered after six weeks showed a nodule of new bone in every instance. The nodules ranged from 2 mm. to 2 cm. in diameter and did not tend to assume an adult type of architecture. In no instance was formation of cartilage noted (fig. 9).

FATE OF BONE DEVOID OF PERIOSTEAL COVERING

Deperiostealized Ribs.—These data are drawn from experiments cited in other connections in this paper, and the procedures need not be described in detail again.

Fig. 8.—This roentgenogram shows the result of an experiment in which, six weeks previously, the intercostal bundles were carefully dissected away from these ribs, leaving the periosteal covering intact. A sterile gauze pack was then inserted between these periostealized ribs and the muscle bundles. A draining sinus formed in the wound, from which bony spicules were extruded. Solution of continuity of ribs is shown with adjacent periosteal new bone, probably stimulated by the local irritation of the pack.

Briefly, in 38 dogs ribs were divested of their periosteal covering and separation was maintained by muscle grafts or by foreign body packs. The ribs were studied microscopically and by roentgenogram at intervals varying from eight days to six weeks. In each instance there was death of the bone with slowly progressive atrophy and absorption by adjacent granulation tissue, which grew in and attempted to revascularize the dead bone. In no case was there definite evidence of new bone developing from the old, although new connective tissue was abundant.

FATE OF OSSEOUS AND OSTEOPERIOSTEAL TRANSPLANTS

Subfascial Implantation of Periosteum-Free Segments of Rib.—In 7 dogs a 2 cm. segment of rib was excised and stripped of its periosteum. This fragment of denuded bone was then implanted into the abdominal wall just beneath the anterior sheath of the rectus abdominis muscle. Hemostasis was secured. One dog died on the ninth day from some other cause, and specimens from the other animals were recovered after six weeks. The nine day implant was apparently dead, the lacunas being empty and fragmentation of the specimen being already present. The 6 specimens recovered after six weeks showed fragmentation and evidences of absorption. Some of these implants were almost entirely absorbed, being represented by tiny spicules embedded in a heavy layer of granulation tissue. Practically all of the lacunas were empty, and the interstices were being invaded by new

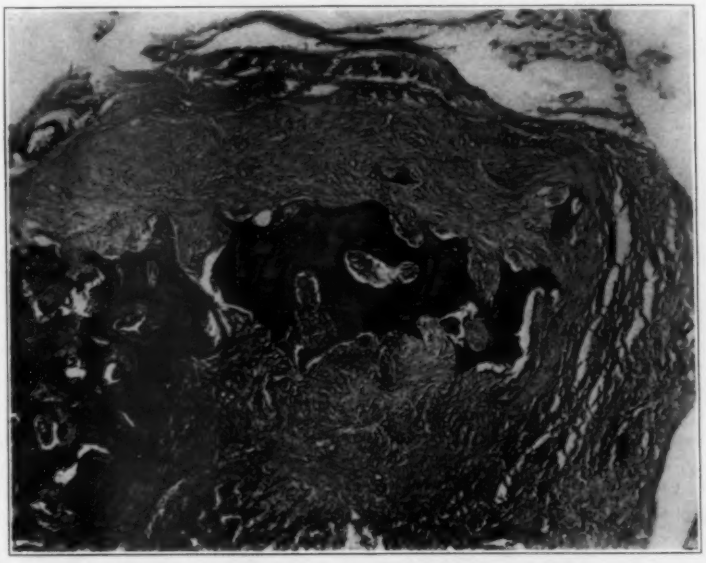

Fig. 9.—This photomicrograph of a fragment of free periosteum, taken six weeks after its subfascial implantation, shows the development of new bone from connective tissue elements.

connective tissue (fig. 10). In 2 instances there was evidence of new osseous formation, but it cannot be definitely stated that this new bone originated from the old. It may be argued that the presence of abundant vascularity and calcium salts leads to metaplasia of the connective tissue.

Subfascial Implantation of Periosteum-Covered Segments of Rib.—In 2 dogs similar implants were made, except that the periosteum was allowed to remain on the graft. After six weeks the specimens were removed. One specimen apparently was living, showed no evidence of absorption and had formed a small amount of new bone under the periosteum. The other specimen had been absorbed almost completely and there was no evidence of the formation of new bone.

EFFECT OF AN UNDERLYING CAVITY ON FORMATION OF BONE

Separation of Periosteum-Covered Ribs from the Intercostal Bundles by Foreign Body Packs.—In an effort to determine whether or not bone will proliferate, as does pleura, in an attempt to obliterate an adjacent cavity, the following experiments were carried out: In 6 dogs the intercostal bundles were carefully dissected from six adjacent ribs, the periosteal covering being left intact. A portion of a celluloid soap dish was then inserted between the endothoracic fascia and the periostealized ribs. Three of the dogs died of erosion of the pleura, pleural effusion and pulmonary collapse. After six weeks the remaining dogs were killed. In 1 dog thickening of the parietal pleura beneath the foreign body had developed. In every instance the ribs were found to be covered by granulation tissue, and nodules of new bone had developed over the surface, apparently growing from

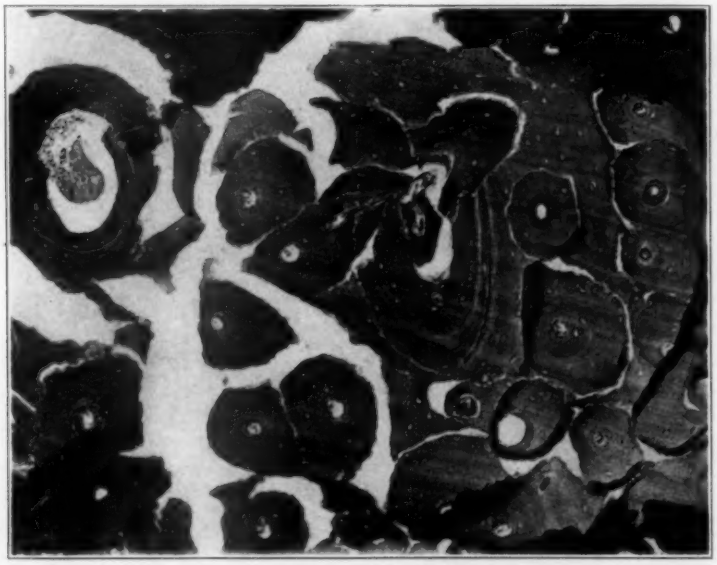

Fig. 10.—This photomicrograph of a deperiostealized graft of bone, taken six weeks after its subfascial implantation, shows it to be dead. The lacunas are empty, and fragmentation is beginning.

the haversian canals (fig. 11). Rather large spurs had formed at the edges of the artificial cavity, but there was no demonstrable evidence of formation of new bone on the inner aspect of the ribs in order to close the cavity. When sectioned, the ribs were seen to be dead, and the follicles were empty. The dead bone was being vascularized and absorbed by adjacent new granulation tissue. In one instance the artificial cavity contained a caseous white material. In the others it contained serous fluid. Aspiration had been necessary in order to remove this fluid on several occasions during the course of the experiment. This experiment did not fulfil its purpose, because the periosteal blood supply from the intercostal bundles was cut off, and apparently the endosteal blood supply is insufficient to maintain viability in the dog's rib.

INHIBITION OF RIB REGENERATION BY CHEMICAL AGENTS

Subperiosteal Rib Resection with Zenker's Solution Applied to the Periosteal Bed.—In 15 dogs a 3 cm. segment of rib was resected subperiosteally. The periosteal bed and the ends of the rib were then treated with freshly prepared Zenker's solution. Care was taken not to use an excess of fluid, and the adjacent tissues were protected as well as possible. Two dogs died of pneumothorax, and Zenker's fluid was found to have caused necrosis and perforation of the pleura. In 1 instance pleuropulmonary adhesions had formed beneath the operative site. Specimens were taken after eight, ten, fourteen, thirty and ninety days. The early specimens were characterized at gross examination and when sectioned by a shaggy, necrotic area representing the periosteal bed. In the later specimens this necrotic tissue had been absorbed, and the sections showed a mass of fresh granulation tissue infiltrated by leukocytes, especially neutrophils. In no specimen was there any evidence of formation of new bone from the periosteal beds. In 3

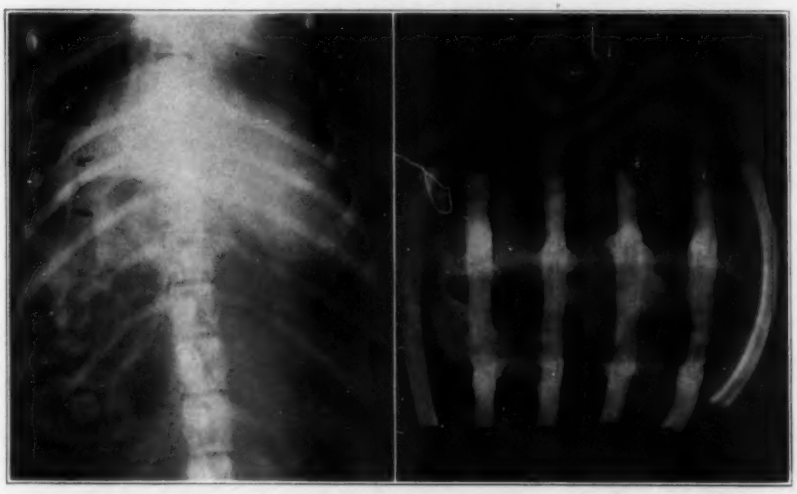

Fig. 11.—The roentgenogram at the left shows the position of the celluloid device forming a subperiosteal extrapleural cavity. This device was placed between the ribs and the pleura, the periosteum being left on the ribs but the intercostal bundles being dissected off. The roentgenogram at the right shows the specimen removed after six weeks, demonstrating slight atrophic changes in the periostealized ribs over the cavity, deprived of their intercostal vascular supply. There is some periosteal new bone.

specimens there was a small spur of new bone at the point of section of the rib. This bone seemed to be developing from connective tissue.

Subperiosteal Rib Resection with Solution of Formaldehyde Applied to the Periosteal Bed.—In 15 dogs a 3 cm. segment of rib was resected subperiosteally, and the periosteal bed was treated with solution of formaldehyde U. S. P. diluted 1 to 10. In 1 dog pleural necrosis occurred, with perforation and death. One dog showed pleuropulmonary adhesions beneath the operative site. The specimens were recovered after eight, ten, fourteen, thirty and ninety days. There was much less necrotic tissue than after the use of Zenker's solution. After the use

of solution of formaldehyde the periosteal bed most often contained a mucoid material of gelatinous consistency. In no instance was there periosteal new bone, and in only 1 instance was there a spur from the end of the rib (fig. 12).

Use of Solution of Formaldehyde in Periosteal Bed After Thoracoplasty.—In 5 dogs a modified thoracoplasty was done, four, five or six ribs being excised subperiosteally. The ends of the ribs and the periosteal beds were then treated with solution of formaldehyde U. S. P. diluted 1 to 10. In 3 of the dogs multiple stage procedures were attempted, but the animals died after the sceond stage. In 1 instance death was due to pleural perforation by the sharp end of a rib. One specimen was obtained after two months. There was no osseous regeneration and but little spur formation. The other specimen was obtained after four months. Healing had taken place by the formation of dense fibrous tissue. There was no evidence of new bone formation. In these animals, as compared with those on

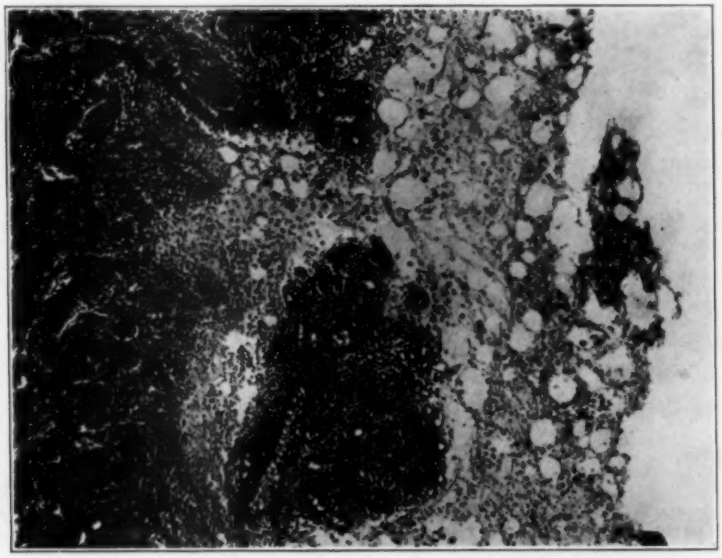

Fig. 12.—This photomicrograph shows granulation tissue and new fibrous tissue, demonstrated by section one month after the periosteal bed was treated with solution of formaldehyde. This reaction is less severe than that seen following the use of Zenker's solution. There is no new osseous formation.

which thoracoplasty was performed without treatment, wound healing was slightly delayed, but this delay was not more than three or four days. In the dogs treated with solution of formaldehyde dyspnea and paradoxic respiratory motion were observed to disappear much earlier than in the untreated dogs. Apparently this resulted because of the stimulation of proliferation in the connective tissue after the application of solution of formaldehyde, causing rigidity of the wall to follow during the first week. This did not interfere with collapse, however, as collapse was found to be much more nearly complete in the dogs treated with solution of formaldehyde. The latter observations cannot be supported by photographic or kymographic proof.

CLINICAL MATERIAL

RIBS OVERLYING EMPYEMA CAVITIES

Chronic Empyema.—In 6 cases of chronic empyema, ranging from three months to several years in duration, ribs were secured for study after unroofing procedures. Roentgenograms in each case showed new bone formation along the inner inferior borders of the ribs. The normal costal contour was lost, and the general shape was changed from the normal ovoid to square or triangular. There was a direct correlation between the duration of the empyema and the amount of new bone laid down. In the cases of empyema of longer duration, normal costal architecture was entirely lost, there being no division into cortex and medulla. There was also a direct correlation between the size of the rib and the

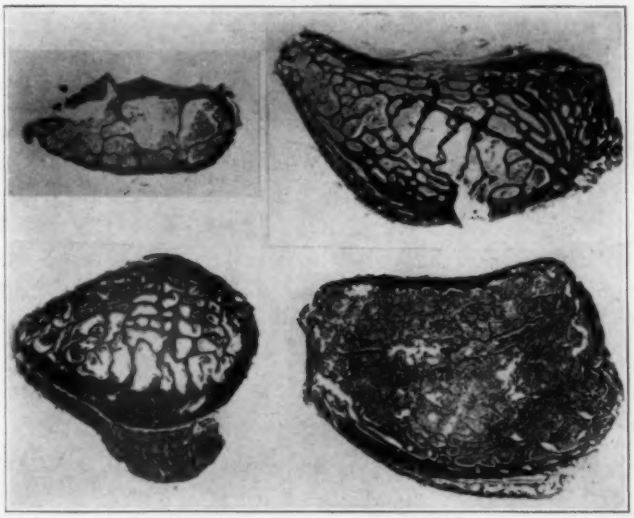

Fig. 13.—These photomicrographs of rib sections from the clinical material show the new osseous formation in cases of empyema thoracis. In the upper left is a section from a normal rib removed at thoracoplasty and studied as a control. Below it is seen the new bone formed in a case of empyema of two months' duration. The rib on the upper right demonstrates the amount of new bone in a case of empyema of four months' duration and below it is a section of rib obtained in a case of empyema of two years' duration. All sections are shown at the same degree of magnification.

duration of the empyema. The new bone apparently was formed subperiosteally and was deposited in successive layers over the empyema cavity (fig. 13).

Acute Empyema.—The ribs in 10 cases of acute empyema were studied by roentgenograms and sections were taken through the resected segments. In all cases the disease was of less than four weeks' duration, and in no case was any new bone demonstrable.

REGENERATION OF RIBS AFTER THORACOPLASTY AND RIB RESECTION

A study of roentgenograms taken after thoracoplasty shows that rib regeneration usually can be demonstrated in three or four weeks after the operation. The regeneration tends to take the form of flat sheets of bone with many synostoses, owing to the fact that the new bone is formed from the flat expanses of periosteum, which do not have their original tubular form. In some instances new bone can be demonstrated as early as two weeks after thoracoplasty, and in certain cases this new bone formation definitely interferes with surgical collapse therapy. In several cases it has been necessary secondarily to excise this regenerated bone in order to achieve adequate collapse from subsequent procedures. Probably, however, more frequent causes of revision of thoracoplasty are (1) inadequate external compression and (2) inadequate original thoracoplasty.

INHIBITION OF REGENERATION

In a series of cases of acute and chronic empyema, abscess of the lung and surgical tuberculosis the periosteal beds have been treated with solution of formaldehyde U.S.P. diluted 1 to 10, and the effect on regeneration of bone has been observed for three months. In this series of about 12 cases, there has been no evidence of new bone formation in 10, even after three months, and this is an interval much longer than is usually allowed to elapse between stages of thoracoplasty. In 2 cases there was some regeneration after four weeks.

With empyema and abscess of the lung, in which healing is normally slow, the disadvantage of having new bone formed before the underlying cavity has closed is obvious. I have seen several cases in which the regenerating rib so tightly encircled the drainage tube as to necessitate a secondary resection.

In the cases of thoracoplasty no delay in the healing of the wound could be noticed, and thus far no contraindication to the use of solution of formaldehyde on the periosteal beds has been demonstrated.

COMMENT

There are many factors which must be taken into consideration in explaining the various conflicting reports found in the literature, and it is probable that when judged by the same criteria these results could be brought into accord. For example, in experimental work the age of the animal is very important, as is the degree of operative trauma to the local vascular supply. Also, in speaking of free bone grafts, it is necessary to consider the size, because whereas small grafts may

readily acquire a new blood supply and grow, larger grafts may become necrotic before such a supply can be established. The vascularity of the site into which the graft is implanted must also be considered. One must remember that much of the original work was done before the days of aseptic surgery and that consequently infection must have modified the results considerably. Too, there has been some discussion as to whether the cambium cells should be classed with the periosteum or with the bone. This would, of course, influence the interpretation of results. Consideration of these and other factors may clear up many apparent discrepancies in reported results. Most reports have been written in support of one of the theories of regeneration of bone without consideration of the fact that each of these theories may obtain under different conditions and in different locations.

The periosteum of the dog's rib is definitely osteogenic, and that the periosteum does not serve merely as a limiting membrane is shown by the fact that in these experiments the periosteum was invariably left as a flat sheet and was not tubulized. It has been observed that in the presence of a good blood supply periosteum tends to form new bone, whereas in the absence of vascularity cartilage or fibrous tissue is formed. This observation probably has some bearing on the question of nonunion of fractures.

The periosteum in every experiment has been found to be a definite anatomic structure. In young animals it is easily stripped from the rib and is capable of producing new bone, but in old animals it is a thin layer, densely adherent to the rib and relatively incapable of forming new bone. Wherever new bone has been formed the periosteum can be seen to be the site of extreme cellular activity. Periosteum is not necessarily a layer made up of specifically osteoblastic cells, however, for regenerated ribs become covered with a layer of fibrous connective tissue which cannot be differentiated from the original periosteum.

In 91 per cent of these experiments new bone could be seen to be developing from connective tissue elements, apparently derived largely from periosteal activity but probably also partially from the adjacent tissues, as fibroblasts cannot be differentiated from osteoblasts. In a relatively small number of instances cartilage had been formed and could be seen to be undergoing ossification in some places. In no instance was the new rib preformed in cartilage.

It does not seem reasonable to suppose, and these experiments do not give evidence, that adult fibrous tissue can become bone by metaplasia or that adult bone cells can escape from their lacunas and become foci for the formation of new bone. It seems quite rational, however, to expect the ubiquitous fibroblast to assume osteogenic prop-

erties under proper conditions of vascularity and availability of calcium. This explains the phenomenon of heterotopic bone formation and may explain the growth of free bone grafts, although the exact role of endosteum and the haversian system cannot properly be evaluated.

The removal of periosteum together with a rib segment effectually inhibited osseous regeneration, and there was no attempt to bridge the defect. The ends of the ribs became rounded, and the marrow cavities were sealed off by fibrous tissue. This probably illustrates the development of nonunion and pseudoarthrosis following a fracture in which the fragments are separated by periosteum over their ends or by interposed soft tissue.

Interposition of a muscle flap or of a foreign body pack between a rib and its periosteum resulted in absorption of the denuded rib and formation of a new rib in the periosteal bed. This indicates not only that the periosteum is capable of laying down new bone but that its normal function is to supply the bone with adequate nourishment. This is borne out by the fact that similar osseous necrosis resulted from destroying the intercostal blood supply to the periosteum. The denuded bone first became atrophic and then became covered by a layer of granulation tissue,[64] which began the work of fragmenting and absorbing the dead bone.

Osseous, periosteal and osteoperiosteal implants into muscle grew with varying degrees of success, seemingly in direct ratio to the ease and speed with which a new blood supply was established. Periosteal grafts grew more frequently than did osseous grafts, as might be expected because of the fact that a thin sheet of periosteum is more easily vascularized than is a segment of dense bone. With regard to free bone grafts, one cannot be sure that the new bone has not developed from elements of the endosteum or from the haversian system.

Costal fractures showed no tendency to heal if the fragments were separated from their periosteum by an interposed flap of muscle. The fragments became eburnated and partially absorbed. There was no evidence of callus from the endosteum, but there was a reaction in the fibrous tissue with consequent immobilization. New bone developed in the periosteal bed beneath the flap. These experiments indicate that the endosteum in the rib of the dog has feeble, if any, osteogenic properties and that the healing of the costal fractures is chiefly dependent on the presence of periosteum on the fragments.

In the experimental series it was seen that early rib regeneration hindered the progress of collapse with the multiple stage type of

64. Phemister, D. B.: Necrotic Bone and the Subsequent Changes Which It Undergoes, J. A. M. A. **64**:211-216 (Jan. 16) 1915.

thoracoplasty. The stages were spaced at biweekly intervals, and new bone had already begun to develop before the next stage was attempted. Complete regeneration of the ribs was the rule in four weeks. These new ribs sometimes showed the presence of spontaneous fractures, probably due to respiratory excursion and usually lacked the normal outward bowing.

Zenker's solution and solution of formaldehyde U.S.P. diluted 1 to 10 when applied to the periosteal beds after resection of ribs were found to inhibit regeneration for at least four months. Zenker's solution exerted a more severe reaction, causing necrosis of tissue, pleural perforations, delayed healing of the wound and, in some instances, pleuropulmonary adhesions. Solution of formaldehyde caused a much less severe reaction, with a consequently lower percentage of morbidity and mortality.

In the experimental thoracoplasties in which solution of formaldehyde was used on the periosteal beds, paradoxic respiratory motion was present for a shorter period than when the treatment was not given, probably because of the greater stimulus to the formation of fibrous tissue given by the formaldehyde. The chest walls of the subjects were actually rigid sooner than those of the untreated subjects. Collapse was more nearly complete in the subjects in which solution of formaldehyde was used, probably because of the absence of regenerated bone. The healing of the wound was delayed only slightly.

Clinically, ribs overlying chronic empyema cavities were found to show new osseous formation on their inner and lower aspects. The entire costal contour and architecture were altered, and the changes seemed to be in direct ratio to the duration of the process. Such new bone formation could not be demonstrated in cases of empyema of less than four weeks' duration, and these changes could not be used to measure the size of the underlying cavity on roentgenoscopic examination.

Early rib regeneration after thoracoplasty was found to interfere with adequate pulmonary collapse in some cases of pulmonary tuberculosis treated by multiple stage thoracoplasty. I believe that this can be obviated by the use of solution of formaldehyde U.S.P. diluted 1 to 10 on the periosteal beds during the first stage of the procedure. This allows for a longer interval between stages, if necessary because of occurrence of traumatic infection or the spread of tuberculosis to the opposite lung. Solution of formaldehyde need not be used in the subsequent stages. No fear of a permanently pliable chest wall need be entertained, because the operative area of the first stage of the procedure is adequately protected by the scapula and by the heavy muscles of the back and shoulder.

CONCLUSIONS

1. Periosteum is definitely osteogenic and is a very important source of blood supply to bone.

2. Periosteum is the most important source of regeneration of bone and its presence is necessary for union in case of fracture.

3. The growth of osseous and periosteal transplants is in direct ratio to their ability to establish an adequate blood supply.

4. Solution of formaldehyde is superior to Zenker's solution as an inhibitor of costal regeneration, the inhibition which it produces lasting for at least four months.

The application of solution of formaldehyde U.S.P. diluted 1 to 10 to the periosteal beds in a series of clinical cases has not been accompanied by delayed healing of the wound or by any other disadvantage. No positive results can be stated as yet, because the series is small and the follow-up interval is too short.

The application of solution of formaldehyde to the periosteal beds is advocated in all resections of the ribs for the drainage of empyema or abscess of the lung. It is also advocated in first stage thoracoplasties, with the reservation that it should not be used in the bed of the first rib because of possible damage to the adjacent nerves and vessels by the formation of scar tissue.

5. The chemical inhibition of rib regeneration should not be employed in the Semb type of apicolysis, because in this operation the new bone aids in maintaining collapse of the lung.

APPENDICITIS AT THE JAMESON MEMORIAL HOSPITAL

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Fifty-one years ago Reginald Fitz, of Boston, read his classic paper on "Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment." It has been estimated that since that time ten thousand papers have been written on the subject.[1] In one sense, certainly, there is little left to be said. Yet, considering the magnitude of the problem and the fact that every hospital plays a part in the fight against appendicitis, I can probably find excuse for describing how the hospital at New Castle, Pa., is coping with the problem.

Appendicitis assumes the proportions of a problem in public health when one realizes that, while it is a disease which if promptly recognized and properly treated should be practically free from mortality, it produces an annual death rate in the United States which equals the combined annual death rates from ectopic pregnancy, pyosalpinx, gallstones and all diseases requiring intervention in the pancreas, spleen and thyroid, nearly equals that from gastric ulcer, duodenal ulcer, intestinal obstruction and gallstones, exceeds that from measles, scarlet fever and whooping cough together, equals that from automobile accidents and nearly equals that from diabetes.[2]

A further reason that has compelled the medical profession to take stock of appendicitis frequently is that many writers until recently were much annoyed by the tendency for the death rate from this disease to increase. The death rate in the United States in 1928 for appendicitis was 15.3 per hundred thousand, while by 1933 it was 18 per hundred thousand. On the other hand, in the "Statistical Bulletin" for August 1936, there is a study on the recent decline in the death rate from appendicitis.[3] This study is based not on the population as a whole but on Metropolitan industrial policyholders. The standardized death rate from appendicitis in this group dropped steadily

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From the Jameson Memorial Hospital.

1. Elkin, D. C., and Glenn, W.: Acute Appendicitis, J. M. A. Georgia **25**: 113 (April) 1936.

2. Wright, T.: Appendicitis: General Survey and Statistics, New York State J. Med. **33**:673 (June 1) 1933.

3. Recent Decline in Appendicitis Death Rate, Statist. Bull., Metropolitan Life Insur. Co. **17**:4 (Aug.) 1936.

from 14.3 per hundred thousand in 1931 to 11.5 in 1935, a decrease of 20 per cent. According to this same source, comparable data for the general population are available and show the same general downward trend.

It is not unlikely that this healthy trend is due to critical analysis of the situation by hospitals, medical societies and interested physicians. It is stated that because of self study and resulting educational propaganda Philadelphia has attained a death rate from appendicitis that is 81 per cent lower than the average of one hundred and seventeen other cites. When allowance is made for errors, this is shown to mean that Philadelphia has made a flat reduction of 75 per cent in its mortality from appendicitis.[4]

The New York Academy of Medicine has instituted a serious study of this problem and its Committee on Public Health Relations has been authorized to make a further study along the lines of the recent investigation of maternal welfare.

It is suggested that every surgeon and the staff of every hospital should prepare to answer the following questions:[5]

1. What mortality do you encounter from appendicitis?

2. In what percentage of cases is operation performed before rupture occurs?

3. In the cases in which rupture takes place, who is the cause of the delay: (*a*) the patient; (*b*) the family physician; (*c*) the surgeon?

4. Are cathartics responsible for the rupture?

5. If so, by whom were they administered: (*a*) the patient; (*b*) the patient's family; (*c*) the druggist; (*d*) the physician?

6. In the cases in which complications occur, has operation been immediate or deferred, and what mortality have you encountered in this special group of cases?

It is with the purpose of self analysis and of answering such questions as these in order to know where they stand on this problem that the staff of the Jameson Memorial Hospital, at New Castle, Pa., has undertaken a study of appendicitis. To gather material for this study it was decided to survey the records of all patients discharged from the hospital in 1935 and 1936 with a final diagnosis of appendicitis.

The total number of admissions to the hospital for this two year period was 5,943. The number of patients for whom a final diagnosis of appendicitis was recorded was 440 for the two years. Not allowing for readmissions or for the fact that some of the patients were not

4. Foltz, J. A.: The Rising Mortality in Appendicitis and What We Are to Do About It, J. Arkansas M. Soc. **33**:49 (Aug.) 1936.

5. Ramsdell, E. G.: Appendicitis: A Challenge, New York State J. Med. **35**:673 (July 1) 1935.

operated on and thus the diagnosis was not proved to be correct, for 1 of every 14 patients who left the hospital appendicitis was at least one of the conditions diagnosed.

Of these 440 patients, 23 (5.2 per cent) were not operated on. These 23 patients were managed by twelve different doctors, 15 (65.2 per cent) of them by surgeons and 8 (34.8 per cent) by internists and general practitioners.

In the group of patients on whom operation was not performed there was a mortality of 8.7 per cent (2 patients). One patient, a 32 year old woman, was moribund on admission. She had been ill for two weeks, and, as far as could be learned, a physician had not been consulted until the fatal generalized peritonitis had set in. She died after five hours, during which time the Ochsner treatment for peritonitis was instituted.

In the other case with a fatal outcome, that of a 79 year old woman, the history, results of physical examination and observations in the laboratory were characteristic of appendicitis. Operation was deferred because the patient presented also auricular fibrillation and edema of the ankles. However, after eight days in the hospital, she died from a cerebrovascular accident. As no autopsy was held, there is no certainty about the abdominal condition, which may well have been an embolic phenomenon.

Another 9.7 per cent (2 patients) of those on whom operation was not performed returned at a later date. One, a 10 year old girl, returned to the hospital ten months after her first admission, having suffered an abdominal attack of two days' duration. The microscopic examination of her appendix was said to show no pathologic condition. The other patient, a 47 year old man, who had been having abdominal upsets for years, returned to the hospital after two months. An appendectomy was done, and microscopically the appendix showed the reaction of chronic inflammation and fibrosis.

One of the 23 patients not submitted to operation had hemophilia. He was a 26 year old white American who four days before admission had diffuse pain in the abdomen, later localized in the right lower quadrant. He experienced nausea and vomiting. He had taken a cathartic by mouth. On admission, his temperature was 101 F. and his pulse rate 100. Moderate tenderness and muscular spasm were found in the right lower quadrant of the abdomen, and a mass was outlined in this area. No rectal examination was recorded. The urine was normal, and the leukocyte count was 15,400 with 86 per cent polymorphonuclear neutrophils. Because of the hemophilia it was deemed wise to treat the patient expectantly, especially since the presence of a mass in the right lower quadrant indicated a tendency toward localization. To relieve his discomfort acetylsalicylic acid and codeine were given. Fluids were administered parenterally and ice bags were applied to the abdomen.

The mass in the right side tended to subside. The temperature ranged between 101 and 104 F. and stayed at normal after the fifteenth day. Daily differential blood counts were made. On the nineteenth day the patient was discharged in good condition.

In the main the patients on whom no operation was performed were treated as follows: Nothing was given by mouth; ice bags were placed on the abdomen, and in some cases enemas were given. Frequent differential blood counts were made.

It is important to ask why operation was omitted in these cases, because it is the consensus of the hospital staff that operation is advisable when appendicitis presents itself. As has been seen, 1 patient was not operated on because age and cardiac decompensation rendered the prognosis unfavorable; a second because his condition was complicated by hemophilia, and a third, because she had diffuse peritonitis and was moribund (she died five hours after admission). Seven more patients were not subjected to surgical intervention because obviously they did not have appendicitis, although it was mentioned in the final diagnosis. Two probably had renal colic; 2 others had pain associated with the onset of menstruation; another 2, it seems probable from the records, had salpingitis. One patient apparently had gastroenteritis from infection caused by food. In 3 cases, in which the symptoms were mild and rapidly subsiding, diagnoses of subacute appendicitis were made and the patients were sent home after one day in the hospital. In 5 cases, with histories of repeated attacks of pain on the right side, diagnoses of chronic appendicitis were made. In 1 of these the patient returned to the hospital two months later and was submitted to operation.

Perhaps operation was not performed in the other cases of chronic appendicitis because the surgeons were acquainted with Bettman's study, made in 1928, which showed that of a series of 5,664 cases in which operation was performed for chronic appendicitis 40 per cent of the patients were unrelieved, 11.6 per cent were made worse and 1.7 per cent died. On the other hand, Charles Mayo pointed out that the day in which appendicitis was classified as of one of two types, the acute and the remunerative, is past. Dr. Mayo believes that there is a variable syndrome which is caused by chronic appendicitis. The problem is to recognize it preoperatively. Barber and Charles Mayo reviewed 100 cases in which they had performed exploration for certain unexplained abdominal symptoms after careful study. In these cases only the appendix was removed, and in each case it was reported to be chronically diseased. Five years later a check was made on the 100 patients. Sixty-nine said that they were cured, 21 that they were materially benefited and 9 that they were not helped. Although 2 of the 9 were better, they felt that the improvement was due to the removal of infected teeth and tonsils.[6]

6. Mayo, C.: Appendicitis, Southwestern Med. **18**:397 (Dec.) 1934.

There were 5 more patients not submitted to operation in the present series whose condition was diagnosed as acute appendicitis. One was a 73 year old woman who had the typical history, tenderness without spasm and leukocytosis. No doubt temporizing measures were employed in her case because of her age and the opinion that her condition was controllable by conservative therapy. Another of these 5 patients returned ten months later in the midst of a second attack. In the cases of the other 3 the history, signs and laboratory findings pointed to acute appendicitis and that was the diagnosis. The reasons for not having operated are not apparent from a study of the records.

A review of the 417 cases in which operation was performed indicates that 20, or 4.8 per cent, of them were those of girls and women from 16 to 42 years of age, submitted to operation for gynecologic diseases, whose appendixes were incidentally removed. Pathologic report on these appendixes indicated that 30 per cent were normal, 60 per cent chronically diseased and 10 per cent subacutely inflamed. There were no deaths in this group.

Another patient, an 18 year old boy, was awakened four hours before admission by a sharp epigastric pain which two hours later centered about the right lower quadrant of the abdomen. He was nauseated and vomited and presented a considerable degree of pain and tenderness over McBurney's point with relative spasm in the right rectus muscle. He had a normal temperature and a leukocyte count of 12,000 with 86 per cent polymorphonuclear cells. He was operated on, but neither the appendix nor the cecum could be found. This patient had an uneventful recovery and was discharged on the ninth day after operation with a diagnosis of unrotated cecum.

There were 17 women who were submitted to operation for appendicitis primarily but who presented cystic ovaries, which were either punctured or wholly or partially removed. Their cases will be considered with the cases in which operation for appendicitis was performed.

Subtracting the 23 cases in which operation was not performed, the 20 cases of gynecologic conditions and the 1 case in which an appendix was not found from the total of 440 cases leaves to be reviewed a series of 396 cases of appendicitis in which operation was performed.

The records show what is indicated by most studies, that appendicitis is primarily a disease of young persons. Sixty-nine and four-tenths per cent of the patients ranged in age from 11 through 30. Eight and eight-tenths per cent were 10 or under. Forty-four and four-tenths per cent ranged from 11 through 20. Twenty-five per cent ranged from 21 through 30. Eight and five-tenths per cent were between 31 and 40. Five and five-tenths per cent were between 41 and 50. Four and two-tenths per cent were between 51 and 60. There were 1 per cent between

61 and 70 and 0.5 per cent between 71 and 75. The youngest patient was 3 years old and the oldest 75. The ages of 8 patients were not recorded.

There were 60.2 per cent women and girls and 39.8 per cent men and boys in the group. However, when only the patients with simple acute appendicitis, with a suppurative, gangrenous or ruptured appendix are considered, excluding those in whom the appendix showed no pathologic condition, was chronically diseased or was subacutely inflamed, there were 99 men and boys and 90 girls and women afflicted, or 10 per cent more of the former.

The average time that elapsed from the onset of the acute attacks in this series until hospitalization was thirty-four and eight-tenths hours, or approximately one and one-half days. While in some of the cases the time elapsed appeared too long, the average is better than that reported by M. Reid and others from Cincinnati,[7] in whose series the average time that elapsed from onset to hospitalization was ninety-one and two-tenths hours. It is significant to note that in the cases of ruptured appendixes in the series reported from Jameson Hospital the average time that elapsed from the onset of illness to hospitalization was sixty-two and two-tenths hours, or two and one-half days, a period almost twice as long as the average elapsed time in all the cases of acute appendicitis considered together. In those cases in which an abscess had formed before the patients' admission to the hospital, an average of one hundred and eight hours, or four and one-half days, had elapsed from the onset of symptoms. Cutting down this interval is one of the ways by which the physician and the patient can attack the problem of complicated appendicitis.

Stanton [8] has shown after a study of 16,424 cases from the literature that when operation is done during the first twenty-four hours of the attack the mortality in experienced hands is almost negligible. When it is done during the first half of the second day the average mortality is from 2 to 3 per cent. For cases in which operation is done after about forty hours the rate tends to rise sharply, so that when the intervention is done on the third day of the attack the operative mortality averages about 10 per cent. In general, operations done on the fourth or the fifth day are even more dangerous than those done on the third day. Beginning with interventions on the sixth day, the operative mortality starts to decline, and when the operation is done on the ninth or tenth day the rate corresponds approximately with that for the second day.

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7. Reid, M. R.; Poer, D. H., and Merrell, P.: A Statistical Study of 2,921 Cases of Appendicitis, J. A. M. A. **106**:665 (Feb. 29) 1936.

8. Stanton, E. M.: Acute Appendicitis, Surg., Gynec. & Obst. **59**:738 (Nov.) 1934.

Fifty-five per cent of the 396 patients submitted to operation stated that they had had previous attacks of appendicitis. When it is noted that in 29.1 per cent of the 189 cases of acute appendicitis in this series the appendix was gangrenous on admission and that in 63 per cent of these it had perforated, it would seem that too many persons are temporizing in the face of a fatal issue by neglecting first attacks.

Of the 396 cases in which operation was done for appendicitis, the condition was proved to be acute in 47 per cent, or 189 cases. In 41 per cent of this number the patients presented the so-called typical history of appendicitis in which there was pain in the epigastrium or about the umbilicus, followed by nausea, vomiting or both and later localized in the right lower quadrant of the abdomen.

Abdominal pain of some type was present in 100 per cent of the cases. Nausea or vomiting or both was associated with 74 per cent of the acute conditions and with less than 50 per cent of the nonacute. Tenderness in some degree was associated with 94 per cent of the acute conditions and with 92 per cent of the nonacute. Some degree of spasm in the right rectus muscle was associated with 62 per cent of the acute and with less than 30 per cent of the nonacute conditions.

Most authorities, it seems, agree that a rectal or pelvic examination is often helpful as an aid in the diagnosis of appendicitis, since tenderness, induration or mass might be presented to the palpating finger. This examination is said to be especially valuable in the case of children. In this series rectal examinations were recorded in only 32 instances, that is, in only 8.08 per cent of the total number of cases in which operation was done. It is interesting that of the rectal and vaginal examinations done 56 per cent gave positive findings, from tenderness to palpable masses. No doubt, many patients had had rectal and pelvic examinations before admission to the hospital, but these were not recorded. When it is not suitable to permit interns to make these examinations, the physicians in charge should be responsible for recording the facts ascertained by such procedures, in order that they may be a part of the completed records of the hospital.

In 17 per cent, or almost one fifth, of the total number of cases in which operation was done, the patient had taken some cathartic by mouth. A total of 69 patients took cathartics, while an additional 4 were given enemas before admission. Of the 9 patients who died, 6, or two thirds, had taken some cathartic by mouth. Fifteen patients with ruptured appendixes had had cathartics by mouth before admission, and a sixteenth had had an enema. Thus in 45 per cent of the cases in which rupture occurred the patients had had some type of intestinal cleansing before hospitalization. It is to be noted also that in 29 other cases of acute appendicitis, in 7 of which the appendixes were gangrenous, the patients had been given cathartics before admission. The figures indicate that 50 per cent of the purges were administered to 45 per cent

of the patients, among whom are included all those in whom the condition was acute and complicated. In the order of frequency the cathartics taken were: castor oil, liquid petrolatum, magnesia magma, magnesium sulfate, magnesium citrate, sal hepatica (a proprietary saline laxative) and mild mercurous chloride. In some instances the doctor who first saw the patient ordered the cathartic. Indeed medical practitioners should heed the present Reginald Fitz of Boston, who said: "Surely, in the early management of appendicitis to keep the bowels quiet should still be the first and last thought of the physician." [9]

The temperatures in the cases of simple acute appendicitis averaged 99.4 F., varying from 97.4 to 102.4 F. The pulse rates averaged 92, ranging from 74 to 122. The leukocyte counts averaged 9,435, varying between 6,450 and 27,900. The polymorphonuclear counts averaged 70.4 per cent, having a low of 56 and a high of 92.

In the cases of more serious involvement including instances of acute appendicitis with suppurative, gangrenous or ruptured appendixes, the temperatures averaged 101.8 F., with a range from 97 to 104.4 F., on admission. The pulse rates averaged 102, varying from 60 to 140. The leukocyte counts averaged 14,475, ranging from 8,100 to 24,650. The polymorphonuclear counts averaged 80 per cent, varying between 57 and 91.

Of the 396 cases in the series in which operation was done, the condition was acute in 189, as substantiated by pathologic diagnosis. Twenty-two of the cases were classified as instances of subacute involvement and 143 as cases of a chronic reaction, which means that infiltration of round cells and scarring or fibrosis had taken place in varying degrees as seen under the microscope. Forty-two appendixes were considered to be without pathologic manifestations. Thus, of the patients in this series, 48 per cent had acute appendicitis, 42 per cent had subacute or chronic appendicitis and 11 per cent had normal appendixes.

The cases of acute appendicitis may be subdivided as follows:

Simple acute	48, or 25%
Acute suppurative	86, or 46%
Acute gangrenous without rupture of appendix	20, or 11%
Acute gangrenous with rupture of appendix	30, or 19%

Among these cases of acute appendicitis, there were 11 instances of localized peritonitis, 12 instances of the formation of abscesses and 17 instances of spreading peritonitis.

There were 102 instances of discrepancy between the clinical and the microscopic diagnosis, that is, according to the pathologist, a 25 per cent error on the part of the surgeons. In 48 per cent of the cases in

9. Fitz, R.: On Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment, New England J. Med. **213**:245 (Aug. 8) 1935.

which these discrepancies occurred, the surgeon made a diagnosis of acute or subacute appendicitis when the pathologist could find only chronic lesions. In 7 per cent, the surgeon made a diagnosis of subacute or chronic appendicitis when the pathologist called the condition acute. In 24 per cent, the pathologist observed evidence of a pathologic condition when the surgeon had made a diagnosis of chronic or subacute appendicitis. In 20 per cent, the surgeon called the involvement acute when the pathologist saw no evidence of a pathologic condition.

The 396 cases of appendicitis in which operation was done in the hospital in 1935 and 1936 were managed by seventeen different surgeons. Of these, seven had 20 or more cases each, or 89 per cent of the total; five, from 2 to 14 each, or 9 per cent, and five, 1 each, or less than 2 per cent.

With reference to the surgical management in the cases studied, the rule has been to operate promptly when a diagnosis of acute appendicitis is made. When a condition is complicated by an appendical abscess, the tendency is to remove the appendix if possible and insert drains. The same procedure is followed in cases of acute perforative appendicitis with peritonitis. Drainage was employed in 17 per cent of all the cases in which operation was done. It appears that the right rectus incision is favored by the staff of this hospital, as it was used 234 times to 140 for the McBurney approach.

All the surgeons in this hospital favor the inversion of the stump of the appendix. This procedure was omitted only occasionally in the presence of an abscess and in some cases of peritonitis. In this connection Charles Mayo says:[6]

> To invert or not to invert, that is the question. Most surgeons who invert do so that they may sleep more soundly, feeling that the danger of blowing out the stump has been obviated. There are four reasons why I do not invert the carbolized stump of the appendix. 1. Dr. Robertson of the section on Pathologic Anatomy at the Clinic has found that invariably, in cases in which appendectomy with inversion of the stump has been done in combination with some other surgical procedure and death has resulted, there is a pus pocket in the inverted stump up to twenty-one days postoperatively. 2. The cultured suture material used to invert the stump, once having run through the intestinal wall, invariably is infected with pathogenic bacteria. 3. Noninversion shortens the surgical procedure, and, fourthly, I have not had occasion to regret not having inverted the stump.

At the Jameson Hospital, chromic no. 1 suture material is generally used to close the abdominal wound. In the majority of cases the skin is closed with clips, and one or two silkworm gut stay sutures are used. In this series there is no record of any disruption of the abdominal wound while the patient has remained in the hospital. In this connection Carlucci[10] made a follow-up study of defects in abdominal wounds following appendectomy. Of 700 patients from Bellevue Hos-

10. Carlucci, G. A.: Abdominal-Wall Defects Following Appendectomy, Ann. Surg. **100**:1177 (Dec.) 1934.

pital, 12 per cent had some degree of defect. A larger percentage of defects was noted in the cases in which approach was through a right rectus incision than in those in which a McBurney incision was used.

The stay in the hospital of the patients in the series ranged from four to one hundred and four days after operation, depending on such factors as the onset of complications, the use of drains and the initial severity of the condition. The average length of stay after operation was twelve and three-tenths days.

The following complications were present when the patients were admitted to the hospital or developed subsequently: There were 2 cases of pregnancy, in 1 of which abortion occurred on the fourth day after operation. There were complications of the chest in 6 cases (fibrinous pleurisy in 1, bronchopneumonia in 3, bilateral lobar pneumonia in 1 and empyema in 1). In 4 of these 6 cases the patients had received general anesthesia (nitrous oxide, oxygen and ether in 3 and nitrous oxide, oxygen and ethylene in 1), and in 2, spinal anesthesia (procaine hydrochloride). There was postoperative infection of the wound in 8 cases, pelvic abscess in 2, thrombophlebitis in 2, pyelitis in 1, cystitis in 1, fecal fistula in 1, pulmonary infarction in 1, otitis media of the left ear in 1, tonsillitis in 2, an abscessed tooth in 1 and infection of the upper part of the respiratory tract in 3. There were 13 patients whose temperature was above 101 F. later than the sixth day after operation, for reasons either not discovered or not recorded. Thus in 11 per cent of the cases in which operation was done there were complications of some sort caused by conditions other than the appendicitis.

Three hundred and seventy-seven patients received general anesthesia, usually with gas-oxygen induction followed by drop ether. A few were anesthetized by gas and oxygen alone or in conjunction with ether vapor. The gas was usually nitrous oxide, but ethylene was frequently used. One patient was given avertin (tribromethanol) supplemented by nitrous oxide and oxygen. Two patients were operated on under local anesthesia produced by procaine hydrochloride. Spinal anesthesia by procaine hydrochloride was used 16 times, or in only 4 per cent of the cases. No deaths attributable to anesthesia occurred.

In the two year period of 1935 and 1936, as has been pointed out, 440 patients were dismissed from the hospital with a diagnosis of appendicitis. The mortality for this whole group was 2.5 per cent. The mortality of 8.6 per cent which occurred in the group of 20 cases in which no operation was done has been discussed earlier in this paper. It was further noted that no deaths occurred among those patients whose appendectomies were only incidental to some other procedure. Of the 396 patients submitted to operation, 9 died, giving a mortality of 2.3 per cent for this group. This rate compares favorably with Davis'

figure of 2.92 per cent in the Providence Hospital in Detroit,[11] with Schullinger's rate of 5.08 per cent from the Presbyterian Hospital in New York,[12] and with Reid's rate of 6.3 per cent from the Cincinnati General Hospital.[7]

The records show that none of the cases with a fatal outcome were among those in which the condition was classified as uncomplicated. In other words, the mortality was zero in the combined cases of nonpathologic, chronic, subacute or simple acute involvement. If the remaining cases, of more severe involvement, are considered, the mortality becomes 6.3 per cent. Of the patients with acute suppurative conditions complicated by appendical abscess, bilateral lobar pneumonia developed in 1, and death occurred on the fourth day after operation; the mortality was thus 1.2 per cent in this group.

The remaining 8 patients who died were all from the group that had an acute gangrenous condition with ruptured appendix, the mortality for this group being 23 per cent. It may also be added that each one of these 8 had spreading peritonitis. Two of them were under a physician's care from the onset of symptoms, but because the initial symptoms were atypical the correct diagnosis was made too late. In all of these cases operation was done promptly after the patient's admission to the hospital, except in 1 in which the diagnosis was not made until an exploratory operation was done, thirty-six hours after admission.

In 17 instances of acute appendicitis with spreading peritonitis 8 of the patients died; the mortality in this group was thus 47 per cent. This compares unfavorably with rates from similar groups, such as 17.02 per cent reported by Schullinger [12] and 16.6 per cent reported by Arnheim and Neuhof.[13] It is to be pointed out, however, that 2 of the patients with diffuse peritonitis who died had other complications. One died on the fifth day after operation, with complicating bronchopneumonia; the other died on the sixty-fourth day, having suffered from a subhepatic abscess and empyema.

SUMMARY AND CONCLUSION

One of every 20 patients with a diagnosis of appendicitis was not operated on.

In 1 of every 25 patients appendicitis was incidental to other disturbances.

Seven of every 10 patients were 30 or younger.

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11. Davis, J. E.; Muske, P. H.; Mulligan, P. L., and Gutov, J.: Appendicitis, J. A. M. A. **108**:1498 (May 1) 1937.

12. Schullinger, R. M.: Acute Appendicitis and Associated Lesions, Arch. Surg. **32**:65 (Jan.) 1936.

13. Arnheim, E. E., and Neuhof, H.: Mortality in Appendicitis, Surg., Gynec. & Obst. **59**:189 (Aug.) 1934.

There were more women with appendicitis than men, but a higher percentage of men had more serious forms of appendicitis.

The average time of thirty-four and eight-tenths hours from onset of symptoms to hospitalization is too long for the best management of appendicitis.

Too many persons go through first attacks of appendicitis without operative intervention.

Only 4 of every 10 patients presented histories typical of appendicitis.

Rectal examinations are important and should be recorded more frequently.

Too many patients receive cathartics for abdominal upsets which turn out to be appendicitis.

One fifth of the patients on whom operation was performed and two thirds of those who died had received cathartics, sometimes administered by the attending physician.

Approximately 5 of every 10 patients had acute appendicitis; 4 of every 10 had subacute or chronic appendicitis, and 1 of every 10 had a normal appendix.

Approximately 1 of every 5 patients whose condition was acute had a gangrenous appendix that had ruptured.

In approximately 1 of every 10 patients with acute involvement the condition was complicated with abscess or peritonitis.

The surgeon and the pathologist disagreed on diagnosis in 1 of every 4 cases.

The usual practice is to operate as soon as a diagnosis of acute appendicitis is made.

Incision is usually made through the right rectus muscle.

The stump of the appendix is inverted whenever this procedure is at all possible.

The average stay in the hospital is twelve and three-tenths days after operation.

In practically 1 out of every 10 cases the condition was complicated by something other than appendicitis.

Gas (nitrous oxide or ethylene), oxygen and drop ether are the usual anesthetics.

The mortality for the patients who were operated on was a small fraction over 2 of every 100.

The mortality for patients with acute gangrenous appendicitis with rupture was a fraction over 2 of every 10.

Death occurred in nearly 5 of every 10 patients with spreading peritonitis.

In view of this high mortality among patients with diffuse peritonitis, perhaps more attention should be given to the problem of devising some other plan of management for these patients. For example, operation might be deferred, as suggested by Arnheim and others.[13]

MODIFIED DOUBLE ENTEROSTOMY (MIKULICZ) IN RADICAL SURGICAL TREATMENT OF INTUSSUSCEPTION IN CHILDREN

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The high mortality following the resection of gangrenous or irreducible intussusception in infants and young children furnishes sufficient reason for a determined and continuous effort to attain an optimal technic. For the treatment of such a lesion a great many surgical methods have been employed. They may be briefly noted as: (1) resection with lateral or end to end anastomosis; (2) resection with double enterostomy (von Mikulicz,[1]) Paul,[2] Hartmann[3]); (3) resection of the intussusceptum through an incision in the intussuscipiens, with or without lateral anastomosis (Barker,[4] Jessett,[5] Maunsell,[6] Coffey[7]); (4) lateral anastomosis about the lesion with secondary resection; (5) ileostomy with secondary resection; (6) lateral anastomosis about the lesion with secondary sloughing or healing (Rutherford,[8] Parry,[9] Montgomery and Mussil[10]); (7) enterectomy of the base of invagination or simple suture after mesenteric ligation, followed by spontaneous

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Dr. Dean Lewis has previously advocated the procedure recorded in this paper, stressing particularly the control of intestinal obstruction and the protection from extensive fluid loss gained by its use. The recent appearance of two consecutive cases in which treatment by this method was successful has stimulated this more detailed report.

1. von Mikulicz, J.: Chirurgische Erfahrungen ueber das Darmcarcinom, Arch. f. klin. Chir. **69**:28-47, 1903.

2. Paul, F. T.: Two Cases of Colectomy, Brit. M. J. **1**:245-246, 1900.

3. Hartmann, H.: Travaux de chirurgie anatomo-cliniques, Paris, G. Steinheil, 1907.

4. Barker, A. E.: A Suggestion for the Treatment of Irreducible Intussusception of the Bowels, Lancet **1**:79-81, 1982.

5. Jessett, F. B.: A Suggestion for the Treatment of Irreducible Intussusception of the Bowels, Lancet **1**:223, 1892.

6. Maunsell, H. W.: A New Method of Intestinal Surgery, Am. J. M. Sc. **103**:245-257, 1892.

7. Coffey, R. E.: Intestinal Intussusception, Ann. Surg. **45**:42-48, 1907.

8. Rutherford, H.: Irreducible Intussusception in the Infant Treated by Ileo-Colic Anastomosis, Brit. J. Child. Dis. **6**:405-410, 1909.

9. Parry, R. H.: The Treatment of Irreducible Intussusception by Lateral Anastomosis, Proc. Roy. Soc. Med. **2**:271-274, 1908-1909.

10. Montgomery, A. H., and Mussil, J. J.: The Treatment of Irreducible Intussusception in Children, Surg., Gynec. & Obst. **51**:415-419, 1930.

sloughing (Oderfeldt,[11] Capelle[12]); (8) incision in the wall of the intussuscipiens to permit manual reduction, followed by one of the aforementioned methods if necessary (Brown[13]). Statistics summarized from various clinics and from various individual reports show the appalling mortality of 70 per cent in 417 cases in which the patients were treated by one type or another of the foregoing operative procedures.

The optimal surgical technic for the treatment of irreducible or gangrenous intussusception occurring in early life should insure the following essential points: (1) rapidity of execution; (2) complete removal of the irreducible or gangrenous bowel; (3) control of the concomitant intestinal obstruction; (4) control of the loss of fluid, and (5) restoration of the continuity of the intestinal canal. Any discussion of these requirements in relation to the majority of the operative procedures outlined is outside the range of my experience. However, among 76 cases of intussusception in which the condition occurred in infants 2 years of age and under and in which the patients were treated in the surgical service of the Johns Hopkins Hospital there have been 6 instances in which resection has been indicated and performed. In all of the operations but 1, a resection of the ileum with end to end anastomosis, immediate resection followed by double enterostomy was the procedure of choice. Of the 6 patients, 3 died—a mortality of 50 per cent. It is the purpose of this paper to record my experience with the Mikulicz type of resection and to discuss in detail a modification in operative technic followed in the two most recent consecutive and successful resections.

REPORT OF CASES

Case 1.—C. B., a white boy aged 10 months, was admitted to the Harriet Lane Home on Jan. 26, 1937, with a history of vomiting, abdominal pain and bloody stools. His illness had begun seventy-two hours previously. His birth, feeding and early development had been normal. He had had pertussis in April 1936 and had had frequent infections of the upper respiratory tract since that time, culminating in pneumonia and bilateral otitis media four weeks prior to this admission.

Seventy-two hours before admission the infant refused his afternoon feeding, and shortly thereafter he vomited. That evening he began to suffer from intermittent cramplike abdominal pain; it came on at hourly intervals and caused him to scream and clutch the side of his crib. He vomited throughout the night, and on the morning of the second day he was given an enema that returned with fecal material mixed with bright red blood. Attacks of pain and vomiting persisted, but they did not appear to be so frequent during the day as they had been

11. Oderfeldt, H., cited by Bickham, W. S.: Operative Surgery, Philadelphia, W. B. Saunders Company, 1924, p. 774.

12. Capelle, W.: Vorschlag einer einfachen und radikalen Operationsmethode bei Darminvagination, Deutsche Ztschr. f. Chir. **243**:745-748, 1934.

13. Brown, H. P., Jr.: Acute Intussusception in Children, Ann. Surg. **81**:637-645, 1925.

during the preceding night. A physician reported normal abdominal findings on physical examination and prescribed castor oil. The child's symptoms became much worse. His mother noticed that he was voiding infrequently. On the day before admission a mass was thought to be palpable in the right lower abdominal quadrant. During the day the child continued to vomit and had four massive bloody stools. With the appearance of a fifth bloody stool on the following morning, hospitalization was advised.

On admission the child's temperature was 98 F., his pulse rate was 140 and his respiratory rate was 28. The white blood count was 12,000, and the hemoglobin content was 96 per cent. The infant was well nourished but dehydrated and washed out, lying quietly on the examining table and unresponsive to painful or noisy stimuli. The skin was dry, with a lemon yellow tinge. The cheeks were flushed, and the lips were cyanotic. The pharynx was sticky and injected. The abdominal wall was soft and relaxed, with evidence of intra-abdominal distention. There was a readily palpable mass extending from the right lower quadrant of the abdomen to the costal margin on the right side and thence across to the midepigastrium. It was sausage shaped, firm and rubbery and was perhaps 4 cm. in its greatest diameter. Palpation elicited no particular pain response from the child. The mass could not be felt by rectum, but the examining finger was smeared with blood. Physical examination otherwise gave negative results. The clinical impression was intussusception, of sixty to seventy-two hours' duration, and pharyngitis.

The infant was seen by the surgical consultant and was given 150 cc. of a 5 per cent solution of dextrose intravenously. Samples of his blood were grouped and matched for transfusion, and he was sent to the operating room for an immediate laparotomy.

Operation.—The operation consisted of resection of an irreducible and gangrenous intussusception and a double enterostomy with lateral anastomosis.

After anesthesia had been induced with ether by the drop method, the child's abdomen was cleaned with a 3.5 per cent solution of iodine followed by 70 per cent alcohol and was draped in the usual fashion. A long midright rectus incision was made. When the peritoneum was opened, many dilated loops of small intestine presented. A mass could be felt in the right side of the abdominal cavity. With some difficulty, this was brought out into the operative wound for inspection. It consisted of an ileocecal intussusception extending to the middle of the transverse colon. The portion of the large bowel at the ring and the entering ileum were bluish black, dull and obviously gangrenous. Tentative attempts to reduce the intussusception manually by milking the distal end of the mass were futile. Resection was commenced by cutting across the ileum, with the actual cautery between crushing clamps, at a point 8 cm. from the beginning of the intussusception. The mesentery of the ileum was divided between Kelly clamps. The cecum and the ascending colon were quite mobile, and after incision of the lateral peritoneum the mass was easily retracted mesially, exposing the mesentery of the large bowel. This was clamped and divided. Division of the transverse colon in its midportion completed the resection. The mesenteric vessels were ligated with no. 1 plain catgut sutures. The ends of the bowel, with clamps attached, were exteriorized in the upper angle of the incision, the colonic stoma being uppermost. At the suggestion of Dr. Dean Lewis, an ileocolic lateral anastomosis was performed at a point 8 cm. from the resected ends of the bowel, an outer layer of continuous fine black silk and an inner layer of no. 1 plain catgut being used. The upper peritoneal angle was closed about the exteriorized bowel with interrupted sutures of no. 1 plain catgut. The remainder of the peritoneum was closed

with a continuous suture of similar material. Four stay sutures of braided silk were laid. The fascial sheath was closed with interrupted figure-of-eight sutures of no. 0 chromic catgut. The edges of the skin were approximated with interrupted sutures of fine black silk.

Postoperative Course.—The child was given a transfusion immediately after the operation with 100 cc. of citrated blood, and a continuous intravenous "drip" of 5 per cent dextrose solution and 1.5 per cent saline solution was started. During the evening he vomited, and continuous gastric lavage was instituted. On the following day his condition rapidly improved, and the gastric siphonage was discontinued. On the third day after the operation water by mouth was given. This was followed by vomiting and by increasing abdominal distention, which became so alarming that the ileostomy was opened. Earlier in the day two stools had been passed by rectum. Relief from distention and from vomiting was immediate, and on the following day feeding by mouth was resumed. The parenteral intake of fluids was discontinued. During the next ten days the status quo was maintained, with drainage from the ileostomy and normal stools about equally divided in amount. The ends of the bowel could have been closed at any time, but this step was deferred because of the presence of an infection in the operative wound. Sixteen days after the operation bronchitis and bilateral otitis media developed. Loss of fluid through the ileostomy increased, the child's weight began to decrease, and his condition became progressively more critical. After twenty-four hours of parenteral intake of fluid the ends of the bowel were inverted with interrupted sutures of fine no. 1 catgut and the skin edges were approximated with silk sutures above the inverted bowel. The improvement after this procedure was dramatic, and the child was discharged on the twenty-eighth day after the operation.

Pathologic Diagnosis.—The diagnosis was ileocecal intussusception with necrosis of bowel.

Case 2.—G. S., a white boy aged 7 months, was admitted to the Harriet Lane Home for Invalid Children on March 17, 1937. The admission note by Dr. William C. Stifler, Jr., of the resident staff, reads as follows: "The patient is a 7 month old white boy, who is admitted to the hospital because of vomiting and the passing of blood by rectum during the past thirty hours. The family history is non-contributory. The mother's labor was difficult, and the delivery of the child was by version and extraction. The neonatal period was normal. The feeding and the intake of vitamins have been fairly adequate. The development has been normal, and the baby has always been well except for a few colds, otitis media a few weeks ago and, since birth, a slight tendency toward constipation, for which he has been given castoria (an aqueous extract of senna with aromatics). Thirty hours before admission, at 6:30 a. m. yesterday, the child became ill very suddenly. He looked sick, whined as if in pain, vomited frequently and began passing by rectum material which apparently consisted of slime and blood, but no fecal material. He was given small amounts of milk and rather large amounts of water and continued to vomit. The vomiting has occurred two or three times every hour, has been unrelated to the milk and water taken by mouth, has been usually projectile, and has been watery and not stained green or brown. The baby has rested in bed very quietly, has whined and has had apparent attacks of pain, has slept little and has continued to look sicker and sicker. Today he has vomited every few minutes. There have been eleven passages of blood and slime by rectum, but no fecal material. No flatus has been observed. A physician was called yesterday morning and again later in the day. He attributed the

blood to straining and said he felt a mass in the abdomen, for which he advised an enema. The enema produced only blood. The physician called again this morning and advised that the parents bring the baby to the hospital.

"The temperature is 99.6 F.; the pulse rate is 160; the respiratory rate is 30. The blood count shows: hemoglobin, 101 per cent; red blood cells, 4,800,000; white blood cells, 11,700.

"Physical examination shows a sick-looking baby who lies very still, cries occasionally, and pays little attention to what is going on about him. He has a washed-out appearance around the eyes. He responds to external stimuli but does not resist examination at all. The breathing is rapid, but there is no cough. The skin is a trifle inelastic but is otherwise normal. The mucous membranes are of good color. There is no cyanosis. The glands are not enlarged. The head and the eyes are entirely normal. Both the ear drums are dull, but not bulging.

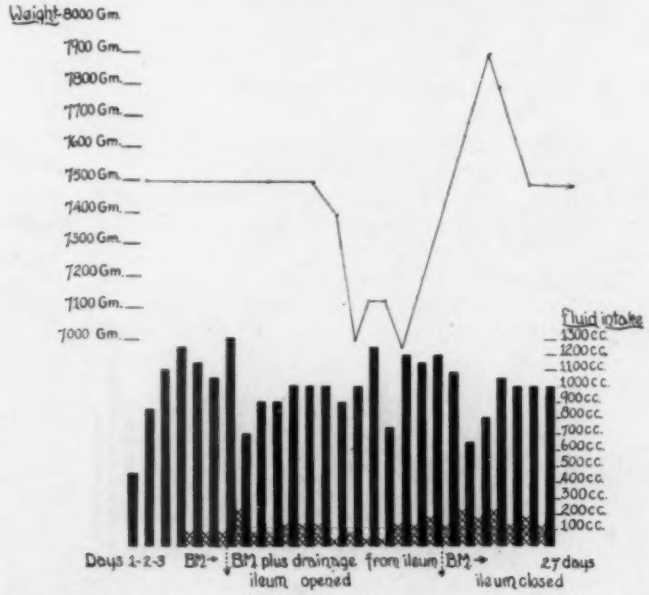

Fig. 1.—Control of fluid loss after resection by modified double enterostomy technic (case 1). Compare with chart 2.

The nose is clear. The mouth and the pharynx show no unusual conditions. The chest is normally developed. The lungs seem clear at percussion and auscultation. The heart is normal; the sounds are of good quality, and no murmurs are heard. The pulse is rapid but well sustained. The abdomen is not distended, is soft and is not tender. Just below the umbilicus and slightly to the left of the midline a mass can be seen and felt. It is about the size of a peach, is fairly firm and is slightly movable. The baby does not seem to object to palpation. On rectal examination one can feel the mass very plainly, and also a depression in the center, which feels like a cervix. No blood is present on the examining finger. The genitalia are normal. The joints and extremities are normal. Neurologic examination was not done.

"Impression: Intussusception, with the ileum far down in the colon, and probably with gangrene of the intestines."

The baby was seen by the surgical consultant and an immediate laparotomy was advised. While the operating room was being prepared, the baby was given 150 cc. of a 5 per cent dextrose solution intravenously and specimens of his blood were grouped for transfusion.

Operation.—The operation consisted of the resection of a gangrenous intussusception and a double enterostomy, with lateral anastomosis.

With the child under anesthesia, obtained with ether by the drop method, the entire abdomen was prepared with a 3.5 per cent solution of iodine and a 70 per cent solution of alcohol and was draped in the usual manner. A long right rectus incision was made. When the peritoneum was opened, the intussusception was at once visible. It was a typical ileocecal intussusception, involving the entire large bowel to the rectosigmoid junction. Reduction was started by gently milking the mass from below and was successfully carried out until the last segment

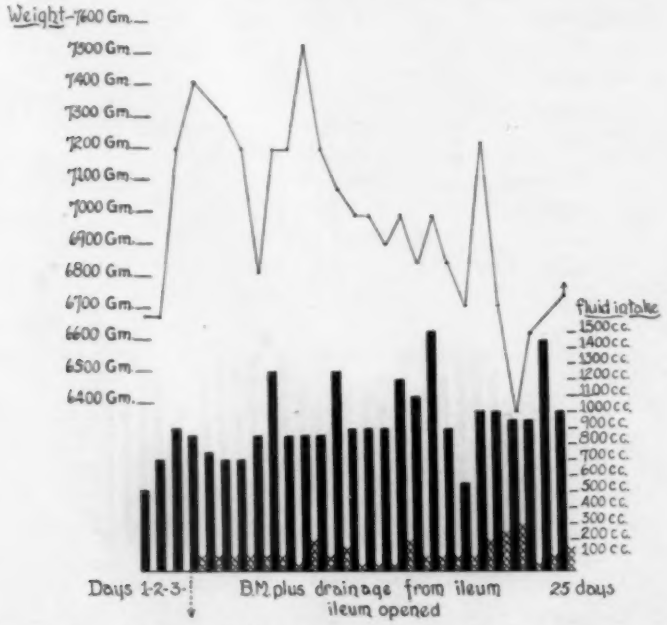

Fig. 2.—Early variation in fluid loss following resection with double enterostomy and failure to restore bowel continuity, recurrent over a period of nine months.

was reached. At this point even considerable pressure produced nothing but numerous rents in the serosa. The anterior wall of the intussuscipiens was incised longitudinally through the constricting ring, in the manner described by Brown. The mass was then forcibly reduced. The distal ileum was obviously gangrenous, and the necrotic area included a portion of the wall of the cecum and the appendix. The distal ileum at a point 10 cm. from the ileocecal valve was cut across with the actual cautery between crushing clamps. Its mesentery was clamped and divided. The peritoneum along the lateral abdominal wall was incised, and the cecum and the ascending colon were retracted mesially. There was an unusually long and mobile cecal mesentery. The mesenteric vessels to the large bowel were clamped and divided. The colon was resected between crushing clamps at a point just distal to the hepatic flexure. In addition to the gangrenous areas

noted, the wall of the entire ascending colon and cecum was edematous, friable and cyanotic. The bowel ends, with clamps attached, were then exteriorized in the upper angle of the incision for a distance of 2 to 3 cm., the colon being uppermost. In accordance with Dr. Dean Lewis' advice as noted in the report of the preceding case, a lateral ileocolic anastomosis was then performed at a point 8 cm. from the ends of the bowel. The usual outer layer of continuous fine black silk was used, followed by an inner layer of continuous no. 1 plain catgut. The upper angle of the peritoneal incision was closed about the double enterostomy with interrupted no. 1 plain catgut sutures and the remainder of the incision was closed with continuous no. 1 plain catgut sutures. Four stay sutures of braided silk were laid. The fascial sheath was closed with interrupted sutures of no. 0 chromic catgut and the skin with interrupted fine silk sutures. The stay sutures were tied over a roll of plain gauze.

The condition of the patient, which was very poor at the beginning of the operation, did not seem to be further affected by the procedure. The operating time was extended to forty minutes because of the prolonged efforts made to reduce the intussusception manually.

Postoperative Course.—The baby was given 120 cc. of a 5 per cent solution of dextrose and 80 cc. of citrated blood before leaving the operating room. On his return to the ward a continuous intravenous "drip" of 5 per cent dextrose solution and 1.5 per cent saline solution was instituted. Twenty-four hours after the operation moderate distention with vomiting occurred. It was controlled by gastric lavage, and it was not deemed necessary to open the ileostomy. Feeding was commenced on the third day after the operation, and was taken hungrily. The parenteral intake of fluids was discontinued. Stools appeared by rectum on the second day after the operation, and on the tenth day, with the patient under light anesthesia (ether again being used) the ends of the bowel were inverted with interrupted no. 1 plain catgut sutures, and the edges of the skin were approximated with interrupted fine silk sutures. The incision healed per primam, and the child was discharged as well on the twenty-eighth day after the operation.

Pathologic Diagnosis.—The diagnosis was ileocecal intussusception, with necrosis of the intestine.

COMMENT

The surgical principle of exteriorization of bowel with immediate or subsequent resection and formation of an abdominal fecal opening was established by the work of Mikulicz [1] in Germany, of Paul [2] in England and of Hartmann [3] in France. The value of the procedure lies in its rapidity of execution and in its prevention of intra-abdominal infection, particularly in the operative attack on tumors of the large bowel, where it has found its sphere of greatest usefulness. Restoration of continuity to the lumen of the bowel depends on obliteration of the spur resulting from the formation of the "gunbarrel" or double enterostomy, and this obliteration may at times offer some difficulty. In order to obviate this technical criticism, Hartmann [3] and Bloodgood [14] early reported having performed the Mikulicz resection with

14. Bloodgood, J. C.: Intestinal Obstruction Due to Volvulus or Adhesions of the Sigmoid Colon, and a Study of the Etiological Factors, Ann. Surg. **49**: 161-182, 1909.

immediate closure of the bowel ends and with the addition of lateral anastomosis. This modified Mikulicz resection has also been advised by Bier [15] in his *System of Surgery* for the treatment of sigmoid tumors. As far as can be ascertained, this modification of the Mikulicz resection has not been used previously in the radical treatment of gangrenous or irreducible intussusception in children.

From my experience with the successful operations recorded, this modification of the Mikulicz resection appears to fulfil adequately the requirements for the optimal surgical technic. It may not, of course,

Fig. 3.—Simple operative technic of modified double enterostomy.

be applicable to all cases of irreducible or gangrenous intussusception, but it appears indicated in all but those of agonal character or those in which final reduction may be obtained by Brown's maneuver. Operative periods of thirty and forty minutes from incision to final dressing indicate that the lateral anastomosis adds little to the time consumed in the performance of a simple Mikulicz resection. Possible absorption from a "side-tracked" intussusception or from bowel left on the abdominal wall is of course eliminated by primary removal of the involved intestine.

15. Bier, A.; Braun, H., and Kümmell, H.: Chirurgische Operationslehre: II. Brustkorb und Bauch, Leipzig, J. Barth, 1912, p. 604.

Worthy of special note is the fact that an ileostomy may be performed above the original point of obstruction if needed. In the first case reported, progressive distention and vomiting promptly subsided following removal of the clamps from the ileal stoma and drainage of the distended small bowel. In the second case an ileostomy was not necessary, and both ends of the bowel were inverted after the need of such drainage had passed, with primary healing.

The fourth and fifth requirements of an optimal method of resection demand control of the loss of fluid and restoration of continuity of the bowel. It is well known that infants are particularly susceptible to the effects of loss of fluid from an ileostomy or from diarrhea. The fluctuating and dangerous state of fluid balance, with concomitant electrolyte imbalance, is graphically illustrated in chart 2, in which is shown the constant loss of intestinal fluid through a simple double enterostomy. Chart 1 (case 1), by contrast, indicates the rapid and permanent control of fluid balance by closure of the ileostomy, followed by primary healing. The lateral anastomosis is effective immediately after the operation and functions as an ileocecal junction as soon as the ends of the bowel are inverted. Fluoroscopic and roentgenographic study of the 2 infants by means of barium enemas, six months and four months after operation respectively, showed obliteration of the inverted or "blind" bowel ends and an unobstructed stoma between the small and the large intestine that presented the roentgenographic picture of an end to end anastomosis.

SUMMARY

Resection, or a similar radical method, for the treatment of irreducible or gangrenous intussusception occurring in early life has a mortality of 70 per cent. In the two most recent consecutive and successful resections in the Johns Hopkins Hospital, the usual Mikulicz procedure has been modified by the addition of a lateral anastomosis. In addition to guaranteeing immediate continuity of the lumen of the bowel this technical modification has proved distinctly valuable in controlling the resultant intestinal obstruction and fluid loss.

TOTAL BILE ACID–CHOLESTEROL RATIO IN HUMAN AND IN CANINE BILE

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The mechanism of the precipitation of cholesterol from bile to form gallstones has received increasing attention in recent years. Since the solubility of cholesterol in bile is dependent, to a great extent, on the presence of bile salts, considerable investigation has been directed toward the bile salt-cholesterol ratio in gallbladder bile. Experimental work on dogs clearly demonstrated that the wall of the inflamed gallbladder absorbs the bile salts of the contents rapidly, leaving an increased concentration of cholesterol.[1] A large number of studies of bile removed from the gallbladder either at operation [1] or at autopsy [2] in cases of disease of the bladder indicated that with the increasing inflammation of the organ the bile salt–cholesterol ratio was progressively lowered. This lowered ratio was obviously due to the decreased concentration of bile salts.

The methods employed by these various investigators for the determination of bile salts were either the Gregory-Pascoe procedure, which is specific for cholic acid only, or the Schmidt-Dart method, which measures only the conjugated bile acids. The investigations of

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From the Surgical Service of Dr. Ralph Colp and the Laboratories of Mount Sinai Hospital.

1. (*a*) Rosenthal, F., and Licht, H.: Die Resorption der Gallensäuren in der normalen und entzündeten Gallenblase, Klin. Wchnschr. **7**:1952, 1928. (*b*) Andrews, E.; Schoenheimer, R., and Hrdina, L.: Chemical Factors and the Role of the Gall Bladder: Etiology of Gall Stones, Arch. Surg. **25**:796 (Oct.) 1932. (*c*) Johnston, C. G.; Ravdin, I. S.; Riegel, C., and Allison, C. L.: Studies on Gall Bladder Function: IX. The Anion-Cation Content of Bile from the Normal and Infected Gall Bladder, J. Clin. Investigation **12**:67, 1933. (*d*) Riegel, C.; Ravdin, I. S.; Johnston, C. G., and Morrison, P. J.: Studies of Gall Bladder Function: XIII. The Composition of Gall Bladder and Calculi in Gall Bladder Disease, Surg., Gynec. & Obst. **62**:933-936. (*e*) Reinhold, J. G.; Ferguson, L. K., and Hunsberger, A., Jr.: The Composition of Human Gall Bladder Bile and Its Relationship to Cholelithiasis, J. Clin. Investigation **16**:367, 1937.

2. Newman, C. E.: Beitrag zum Studium der Gallenniederschlags-und Gallensteinbildung, Beitr. z. path. Anat. u. z. allg. Path. **86**:187, 1931.

Wieland and Revery [3] and our own determinations [4] demonstrated the presence of large amounts of desoxycholic acid in human bile. The Schmidt-Dart method was shown to be often fallacious, since by it about 20 per cent of free bile acids could be demonstrated to be present in normal bile while in pathologic bile the results often showed a high ratio due to the presence of an alcohol-soluble material containing amino-nitrogen. Consequently, the bile salt–cholesterol ratio obtained by these methods tends to be inaccurate. Marked qualitative differences occur in pathologic bile, for occasionally cholic acid is absent from the bile while at other times only free bile acids are present. These factors tend to nullify relative figures representing the bile salt-cholesterol ratio. Reinhold and his co-workers,[1] who have carefully limited themselves in their work to the determination of the cholate-cholesterol ratio, have clearly indicated the difficulty of determining the true bile salt-cholesterol ratio.

Spanner and Bauman [5] showed that the solubility of cholesterol is about four times as great in a 3 per cent solution of the sodium salt of desoxycholic acid as in one of the sodium salt of cholic acid. This faculty of desoxycholic acid to hold cholesterol in solution seems to be dependent on its ability to form addition compounds with cholesterol.[6] Therefore, the determination solely of the amount of cholic acid in the bile appears to be of minor importance in evaluating the factors which keep cholesterol in solution.

A series of bile acid and cholesterol analyses were made of a large number of specimens of bile from the gallbladder and from common duct fistulas to ascertain the fundamental factors determining the solubility of cholesterol in bile. Advantage was taken of a method which determined in each sample of bile the amount of cholic acid, of desoxycholic acid and of total bile acids as well as the content of conjugated bile acids and of free bile acids.[7] It was felt that a more accurate picture of the true bile acid-cholesterol ratio would be obtained as a result. In addition, for purposes of comparison with previous reports,

3. Wieland, H., and Revery, G.: Untersuchungen über die Gallensäuren: XXI. Zur Kenntnis der menschlichen Galle, Ztschr. f. physiol. Chem. **140**:186, 1924.

4. (*a*) Colp, R., and Doubilet, H.: Differential Analysis of Bile Acids in Human Gallbladder Bile, Arch. Surg. **33**:913 (Dec.) 1936. (*b*) Doubilet, H., and Colp, R.: Differential Analysis of Bile Acids in Human Bile from Fistulas, ibid. **34**:149 (Jan.) 1937.

5. Spanner, G. O., and Bauman, L.: The Behaviour of Cholesterol and Other Bile Constituents in Solutions of Bile Salts, J. Biol. Chem. **98**:181, 1932.

6. Wieland, H., and Sorge, H.: Untersuchungen über die Gallensäuren, Ztschr. f. physiol. Chem. **97**:1, 1916. Andrews, Schoenheimer and Hrdina.[1b]

7. Doubilet, H.: Differential Quantitative Bile Acid Analysis in Bile and in Duodenal Drainage, J. Biol. Chem. **114**:289, 1936.

the cholic acid-cholesterol ratio (Gregory-Pascoe method) as well as the conjugated bile acid-cholesterol ratio (Schmidt-Dart method) was estimated.

PROCEDURE

The specimens of bile were obtained either from the gallbladder at operation (by aspiration) or from hepatic fistulas drained daily after the operation. In the latter cases the amount needed in making the determinations was taken from the whole twenty-four hour collection. The amounts of cholic acid, desoxycholic acid, total bile acids and conjugated bile acids were determined by a method previously described.[7] The amount of cholesterol was estimated by the method of Elman and Taussig.[8]

Two hundred and ninety-one analyses were made. These may be classified as follows according to the source of the bile examined.

A. Gallbladder Bile.

1. Bile collected from apparently normal human gallbladders. In addition to 3 specimens of bile obtained at operation, there were 2 specimens of "B" bile obtained by duodenal tube and 1 specimen obtained at autopsy immediately after death (6 analyses).
2. Gallbladder bile obtained in cases of carcinoma of the pancreas (13 analyses).
3. Gallbladder bile obtained at the time of operation in cases of chronic cholecystitis (diagnosis proved pathologically). The gallbladders were divided into two subgroups:
   (*a*) Gallbladders visualized after the injection of tetraiodophenolphthalein (21 analyses).
   (*b*) Gallbladders not visualized by means of tetraiodophenolphthalein (10 analyses).
4. Gallbladder bile obtained in cases of acute cholecystitis:
   (*a*) Early acute cholecystitis (10 analyses).
   (*b*) Hydrops of the gallbladder (7 analyses).
5. Gallbladder bile obtained in cases of pathologic conditions of the liver (8 analyses).

B. Bile Obtained Postoperatively from Fistula Drainage.

6. Hepatic bile obtained in cases of carcinoma of the pancreas (2 cases; 6 analyses) and of miliary tuberculosis (1 case; 2 analyses).
7. Hepatic bile obtained in cases of calculous cholecystitis associated with choledocholithiasis (13 cases; 39 analyses).
8. Hepatic bile obtained in cases of stricture of the choledochus, operation being performed eight months after the primary cholecystectomy (1 case; 7 analyses).
9. Hepatic bile obtained in cases of acute pancreatitis (3 cases; 16 analyses).
10. Hepatic bile obtained in cases of different types of hepatitis and cholangitis (8 cases; 42 analyses).
11. Hepatic bile obtained after administration of bile salts (2 cases; 46 analyses).

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8. Elman, R., and Taussig, J. B.: The Quantitative Determination of Cholesterol in Bile, J. Lab. & Clin. Med. **17**:274, 1931.

12. Hepatic bile obtained to determine the effect on the bile acid-cholesterol ratio of variations in diet (1 case; 7 analyses).

C. Canine Bile.

13. Gallbladder bile obtained from dogs (8 analyses).

14. Hepatic bile (McMaster fistula) obtained from dogs (2 dogs; 43 analyses).

RESULTS

Bile from Gallbladders Normal in Appearance.—Three analyses were made in cases in which no evidence of disease of the gallbladder or liver was present either at operation or in the subsequent clinical course (table 1). In addition the analyses are presented of 2 samples

TABLE 1.—*Bile from Gallbladders Normal in Appearance.*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio				Comment
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	
32	0.400	3.33	4.33	7.66	6.16	8.3	10.8	19.1	15.4	Recurrent attacks of epigastric pain; no pathologic condition
71	0.666	2.75	5.59	8.34	7.80	4.1	8.1	12.5	11.7	Symptoms relieved by appendectomy
108	0.229	1.58	5.96	7.54	4.48	7.0	26.0	33.0	19.5	Symptoms relieved by appendectomy
G.	0.156	1.41	1.16	2.57	....	9.0	7.4	16.4	....	"B" bile by duodenal tube; gallbladder normal by roentgen visualization
M.	0.243	1.09	2.39	3.48	....	4.5	9.9	14.4	....	"B" bile by duodenal tube; gallbladder normal by roentgen visualization
P.	0.266	1.89	4.31	6.20	0.33	7.1	16.2	16.2	1.2	Bile obtained 3 hr. after death following colonic resection
Average ratio.....						6.6	13.1	19.7	12.2	

of "B" bile obtained from patients who had no clinical or roentgenologic evidence of disease of the gallbladder. One analysis of gallbladder bile obtained soon after death is also presented. These analyses are presented to give some idea of the composition of normal bile. The average total bile acid-cholesterol ratio was found to be 19.7. The normal bile acid-cholesterol ratio is probably close to 20, as was evidenced subsequently by the examination of hepatic bile.

Gallbladder Bile Obtained in Cases of Carcinoma of the Pancreas with Complete Obstruction.—The first 8 analyses of bile obtained from patients with complete obstruction in an early stage gave an average ratio of total bile acids to cholesterol of 23.9. The last 5 analyses were on bile obtained from patients in whom prolonged obstruction had caused an absorption of the greater part of the bile salts and pigment

(the early stage of "white bile"). The total bile acid-cholesterol ratio was 18.8, only a slight decrease from that in the first group. The average figure, then, for the total bile acid-cholesterol ratio is 21.6, agreeing closely with the figures given in table 1 for the bile acid-cholesterol ratio in bile from normal gallbladders.

Gallbladder Bile Obtained in Cases of Chronic and Acute Cholecystitis.—In the cases in which the gallbladder was visualized after the injection of tetraiodophenolphthalein, the average total bile acid-cholesterol ratio was found to be 13 (table 3). The fact that the dye could enter the gallbladder and be concentrated sufficiently for visualization indicated that the gallbladder was functioning, that is, that it could fill and empty itself and could concentrate the bile fairly well. The cholesterol concentrations averaged 0.540 per cent. This is rather high when compared with the concentration of 0.360 per cent obtained in cases of early obstruction (table 2). The bile acid concentration, of 4.96 per cent, was lower than that which has been reported as normal.[9] An important question was raised: Had the bile acids been partially absorbed by the chronically inflamed gallbladder wall, or was the hepatic bile lower in bile acid concentration when it entered the gallbladder?

TABLE 2.—*Gallbladder Bile Obtained in Cases of Carcinoma of the Pancreas with Obstruction*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
Early obstruction:									
U	0.068	0.87	1.16	2.03	0.83	12.8	17.0	29.8	12.2
E. R	0.097	1.70	1.40	3.10	2.66	17.6	14.4	32.0	27.4
38	0.600	4.25	5.50	9.75	8.86	7.1	9.1	16.2	14.7
86	0.352	3.63	2.53	6.16	5.92	10.3	7.2	17.5	17.0
116	0.666	6.13	6.89	13.02	6.82	9.2	10.3	19.5	10.2
122	0.096	1.70	1.40	3.10	2.66	17.7	14.6	32.3	27.7
135	0.519	4.55	6.63	11.18	3.63	8.7	12.8	21.5	7.0
136	0.494	6.74	4.60	11.34	7.41	13.6	9.3	22.9	15.0
Average	0.360	3.7	3.8	7.46	4.85	12.1	11.8	23.9	16.4
Advanced obstruction:									
55	0.003	0.03	0.11	0.14	0.12	10.0	36.6	46.6	40.0
127	0.008	0.015	0.11	0.125	0.15	1.9	13.7	15.6	28.7
137	0.026	0.09	0.02	0.11	0.19	3.5	0.8	4.3	7.3
141	0.106	0.26	0.22	0.48	0.57	2.4	2.1	4.5	5.4
144	0.074	0.95	0.37	1.32	1.00	13.0	5.0	18.0	13.5
Average	0.040	0.27	0.17	0.43	0.40	6.2	12.6	18.8	17.0
Total average	0.240	2.4	2.4	4.8	2.9	9.8	11.8	21.6	16.6

Bile obtained in cases in which the gallbladder was not visualized after the oral administration of dye (table 4) was found to have a total

9. Hammarsten, O.: A Text-Book of Physiological Chemistry, New York, J. Wiley & Sons, 1906, p. 275.

bile acid-cholesterol ratio of 7.7. This is definitely lower than the values found when physiologic function of the gallbladder was preserved. The average cholesterol content in this group was 0.452 per

TABLE 3.—*Gallbladder Bile Obtained in Cases of Chronic Cholecystitis (Gallbladders Visualized After Injection of Tetraiodophenolphthalein)*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
40	0.732	3.33	7.02	10.45	7.41	4.5	9.6	14.1	10.1
44	1.500	0.61	1.81	2.42	2.39	0.4	1.2	1.6	1.5
56	0.158	1.31	4.89	6.20	1.38	8.3	31.0	39.3	8.8
64	0.441	1.58	1.58	5.24	1.77	3.6	8.3	11.9	4.0
79	1.320	1.93	1.93	7.36	5.52	1.4	4.1	5.5	4.2
83	0.217	1.41	1.41	3.57	3.23	6.4	10.0	16.4	14.9
84	0.022	0.12	0.12	0.47	0.32	5.4	16.0	21.4	1.41
95	0.833	1.99	5.07	7.06	5.05	2.4	6.1	8.5	6.0
99	0.148	0.86	0.63	1.49	2.34	5.8	4.2	10.0	16.0
102	0.769	2.78	6.33	9.01	5.38	3.6	8.3	11.9	7.0
103	0.764	1.31	5.96	7.27	3.73	1.7	7.8	9.5	4.8
117	0.227	1.10	1.16	2.26	0.20	4.9	5.1	10.0	0.9
124	0.484	2.26	6.40	8.66	5.77	4.7	13.2	17.9	12.0
128	0.735	2.90	8.71	11.61	6.79	3.9	11.8	15.7	9.2
129	0.422	0.62	3.06	3.68	1.95	1.4	7.2	8.6	4.6
134	0.056	0.10	0.64	0.74	0.06	1.8	11.4	13.2	1.0
138	0.392	1.22	5.11	6.33	3.75	3.1	13.0	16.1	9.5
145	0.851	1.74	2.26	4.00	3.50	2.0	2.7	4.7	4.1
147	0.312	1.87	2.13	4.00	3.01	6.0	7.0	13.0	9.6
148	0.377	1.88	3.62	4.50	....	2.3	9.6	12.0	...
S. K	0.513	1.75	2.72	4.47	1.31	3.4	5.3	8.7	2.5
Average	0.540	1.51	3.45	4.96	3.24	3.7	9.3	13.0	7.2

TABLE 4.—*Gallbladder Bile Obtained in Cases of Chronic Cholecystitis (Nonvisualized Gallbladders)*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
41	0.058	0.22	0.35	0.57	0.42	3.8	6.0	9.8	7.2
47	0.581	1.82	4.48	6.30	4.62	3.1	7.7	10.8	7.9
48	0.845	2.20	4.74	6.94	1.96	2.6	5.6	8.2	2.3
65A	0.540	1.37	2.84	4.21	3.00	2.6	5.2	7.8	5.5
88	0.663	1.94	2.80	4.74	4.16	2.9	4.2	7.1	6.3
89	0.463	0.91	2.24	3.15	3.04	2.0	4.8	6.8	6.6
118	0.178	0.50	0.58	1.08	....	2.8	3.2	6.0	...
139	0.126	0.71	0.64	1.35	0.81	5.6	5.1	10.7	6.4
146	0.412	1.20	1.64	2.84	2.79	2.9	4.0	6.9	6.7
C. C	0.655	0.73	1.39	2.12	1.38	1.1	2.1	3.2	2.1
Average	0.452	1.16	2.17	3.33	2.22	2.9	4.8	7.7	5.7

cent, slightly lower than in the cases reported in table 3 (0.540 per cent). The decrease in the amount of total bile acids, however, brought the ratio down to 7.7.

In cases of acute cholecystitis (table 5) the total bile acid-cholesterol ratio was found to average 6, slightly lower than in cases of advanced

chronic cholecystitis. The figures for cholesterol gave an average of 0.546 per cent, and those for the total bile acids an average of 2.15 per cent. These figures seem to indicate that in acute cholecystitis the lowered bile acid concentration is due to a rapid selective absorption of bile acids, which leaves behind a relatively increased concentration of cholesterol.

TABLE 5.—*Gallbladder Bile Obtained in Cases of Acute Cholecystitis*

		Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
Case	Cholesterol, %	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
34	0.080	0.14	0.34	0.48	1.15	1.7	4.2	5.9	14.4
35	0.105	0.12	0.93	1.05	0.99	1.1	8.8	9.9	9.4
81	0.857	0.73	1.39	2.12	1.26	0.8	1.6	2.4	1.4
90	0.780	1.25	7.09	8.34	7.03	1.6	9.0	10.6	8.9
111	0.506	0.18	0.12	0.30	0.03	0.3	0.2	0.5	0.06
120	0.470	0	0.50	0.50	0	0	1.0	0	0
123	0.126	0.57	1.38	1.95	0.76	4.5	10.9	15.4	6.0
130	0.155	0.36	0.91	1.27	0.69	2.3	5.8	8.1	4.4
143	1.625	0.08	0.81	0.99	0.64	0.04	0.5	0.54	0.4
151	0.750	1.58	3.05	4.63	5.58	2.1	4.1	6.2	7.4
Average	0.546	0.5	1.65	2.15	1.81	1.4	4.6	6.0	5.2

TABLE 6.—*Gallbladder Bile Obtained in Cases of Hydrops of the Gallbladder*

		Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
Case	Cholesterol, %	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
66	0.016	0	0	0	0	0	0	0	0
82	0.012	0	0	0	0	0	0	0	0
119	0.500	0	0	0	0.52	0	0	0	1.0
121	0.272	0	0	0	0.23	0	0	0	0.8
132	0.063	0	0	0	0.34	0	0	0	5.4
149	0.003	0	0	0	0	0	0	0	0
150	0.067	0	0	0	0	0	0	0	0
Average	0.133	0	0	0	0.15	0	0	0	1.0

Table 6 presents the analyses made in 7 cases of hydrops of the gallbladder. These results apparently indicate that a fairly large concentration of cholesterol remains after the bile acids have been completely absorbed. The cholesterol content may be very high. Thus, in case 119 the cholesterol concentration was 0.500 per cent. A number of analyses of the protein content of the hydropic fluid indicated that high cholesterol content was usually associated with a high protein concentration. In cases in which the contents of the gallbladder were thin and watery, as in case 149, the cholesterol concentration was very low. Although neither cholic nor desoxycholic acid could be detected, analysis

by the Schmidt-Dart method for conjugated bile acids occasionally yielded positive results, due to the presence in pathologic bile of an alcohol-soluble material yielding aminonitrogen.[4]

Gallbladder Bile Obtained in Cases of Disease of the Liver.—This series of 8 analyses (table 7) indicates that after severe hepatic injury the excretion of cholesterol tends to be very low. The gallbladder bile in the case of B, in which diagnosis of acute hepatitis was made on the basis of biopsy of material from the liver, was found to have a

TABLE 7.—*Gallbladder Bile Obtained in Cases of Disease of the Liver*

		Bile Acid Percentage				Bile Acid-Cholesterol Ratio				
Case	Cholesterol, %	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Comment
B.	0.055	1.24	5.07	6.31	0.33	22.5	91.3	113.8	6.0	Acute hepatitis
S.	0.017	0.13	0.76	0.89	0.40	7.7	44.7	52.4	23.5	Bile obtained at autopsy from patient with cirrhosis of liver who died in cholemia
131	0.030	0.60	2.30	2.90	1.20	20.0	77.0	97.0	40.0	Normal gallbladder; large liver; fever; hepatitis (?)
133	0.235	3.70	5.25	8.95	5.05	15.7	22.3	38.0	21.5	Jaundice; swollen liver with precipitated pigment in bile ducts; serous hepatitis (?)
105	0.073	1.65	2.23	3.88	2.75	22.6	30.5	52.1	37.7	Operation after acute pain in right upper quadrant and fever; thin-walled gallbladder containing stones
31	0.015	0.15	0.05	0.20	0.52	10.0	3.3	13.3	34.7	Cholangitis; atonic gallbladder containing thin bile
40	0.034	0.22	0.35	0.57	0.36	6.5	10.3	16.8	10.6	Cholangitis; atonic gallbladder containing thin bile
46	0.015	0.04	0.81	0.85	0.26	2.6	54.0	56.6	17.3	Acute pancreatitis with biliary obstruction; normal gallbladder containing thin bile

high concentration of bile acids. The gallbladder, which was edematous and glassy in appearance, had evidently strongly concentrated the dark bile present. In spite of this, the cholesterol content was only 0.055 per cent, giving a total bile acid-cholesterol ratio of 113.8. The content of conjugated bile acids was typically low.[4] As a result, the conjugated bile acid-cholesterol ratio was only 6. In the case of S, bile was obtained immediately after death, the patient dying in cholemia. Although the total bile acid concentration was only 0.89 per cent, the cholesterol content was so low (0.017 per cent) that the ratio was 52.4. In case 131 an enlarged liver with an apparently normal biliary tract was found at operation. Unfortunately, biopsy of the liver was not done, so that the diagnosis of hepatitis was problematic. In case 133, that of a male

patient suffering from jaundice and pruritus, operation revealed an enlarged congested liver but a normal gallbladder. A biopsy of tissue from the liver revealed a morphologically normal parenchyma, but the fine bile ducts contained precipitated pigment. Subsequent studies with iodized poppyseed oil showed the entire biliary tract to be extremely narrowed. This may have been the result of swelling of the surrounding parenchyma, a condition described by Eppinger under the term "serous hepatitis." In this case the total bile acid-cholesterol ratio was 38. In case 155 operation was performed immediately after an attack of severe pain and tenderness in the right upper quadrant of the abdomen, accompanied by high fever. At operation a thin-walled noninflamed gallbladder containing stones was found. The liver was enlarged. The total bile acid-cholesterol ratio was 52.1. In both case 31 and case 40, a large atonic gallbladder containing thin bile was found.

TABLE 8.—*Hepatic Bile Obtained in Cases of Noncalculous Disease*

			Bile Acid Percentage				Bile Acid–Cholesterol Ratio				
Case	Day After Operation	Cholesterol, %	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Comment
57	15th	0.033	0.26	0.22	0.48	0.39	7.9	6.3	14.2	11.8	Carcinoma
	17th	0.036	0.24	0.22	0.46	0.39	6.7	6.1	12.8	11.1	of pancreas
121	2d	0.005	0.04	0.11	0.15	0	8.0	22.0	30.0	0	Carcinoma
	3d	0.006	0.01	0.05	0.06	0.06	1.7	8.3	10.0	10.0	of pancreas
	6th	0.016	0.03	0.07	0.10	0	0.8	4.4	6.2	0	
	20th	0.023	0.12	0.35	0.46	0.26	5.2	15.2	20.4	11.3	
52	15th	0.029	0.20	0.52	0.72	0.55	6.9	17.9	24.8	18.9	Miliary
	19th	0.020	0.14	0.72	0.86	0.46	7.0	36.0	43.0	23.0	tuberculosis

In these 2 cases biopsy of the liver showed considerable pericholangitic cellular infiltration and fibrosis. Both the cholesterol and the bile acid concentration were low, giving a ratio of 13.3 and 16.8 respectively. In case 46 operation was performed for sudden biliary obstruction due to acute pancreatitis. The gallbladder, containing thin bile, appeared normal. The total bile acid-cholesterol ratio was 56.6, owing to the very low concentration of cholesterol. These results suggest that when severe injury of the liver has occurred, as a result of inflammation, of degeneration or of acute obstruction, the cholesterol concentration of the gallbladder bile tends to be extremely low.

Hepatic Bile Obtained in Cases of Noncalculous Disease.—Three analyses were made in cases in which hepatic drainage was carried out for noncalculous disease (table 8). In case 57 and in case 121 drainage was done for carcinoma of the pancreas with obstruction. The patient in case 52, after an operation for acute pain in the right upper quadrant of the abdomen associated with high fever, was found to have miliary tuberculosis. In case 57 the total bile acid-cholesterol ratio was found

to be 14.2 and 12.8 on the fifteenth and the seventeenth day respectively. In case 121 the bile gave a total bile acid-cholesterol ratio of 30 immediately after the release of obstruction, but on the twentieth day the ratio was 20.4. In case 52 the total bile acid-cholesterol ratio

TABLE 9.—*Hepatic Bile Obtained in Cases of Calculous Cholecystitis Associated with Choledocholithiasis*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
139	1st	0.101	0.05	0.04	0.09	0.25	0.5	0.4	0.9	2.4
	10th	0.075	0.28	0.09	0.37	0.49	3.7	1.2	4.9	6.5
	19th	0.094	0.28	0.57	0.84	0.54	2.9	6.1	9.0	5.7
	26th	0.133	0.24	0.64	0.88	0.72	1.8	4.8	6.6	5.4
S. B.	68th	0.079	0.27	0.19	0.46	0.73	3.4	2.4	5.8	9.2
111	10th	0.138	0.15	0.51	0.66	0.81	1.1	3.7	4.8	5.9
	12th	0.077	0.14	0.46	0.60	0.70	1.8	6.0	7.8	9.1
	13th	0.063	0.07	0.19	0.26	0.32	1.1	3.0	4.1	5.1
M. F.	3d	0.004	0.007	0.035	0.04	0.06	1.7	8.7	10.4	15.0
	6th	0.020	0.03	0.12	0.15	0.13	1.5	6.0	7.5	6.5
	13th	0.053	0.06	0.16	0.22	0.27	1.1	3.0	4.1	5.1
	29th	0.013	0.01	0.13	0.14	0.16	0.7	10.0	10.7	10.7
J. J.	1st	0.092	0.19	0.67	0.86	0.36	2.1	7.3	9.4	3.9
	5th	0.082	0.07	0.21	0.28	0.26	0.8	2.6	3.4	3.2
	13th	0.076	0.09	0.30	0.39	0.22	1.2	4.0	5.2	5.1
M. K.	8th	0.076	0.27	0.30	0.57	0.37	3.5	3.9	7.4	7.5
S. M.	1st	0.035	0.05	0.37	0.42	0.13	1.4	10.6	12.0	3.7
	8th	0.137	0.50	1.25	1.15	0.92	3.6	9.1	12.7	6.7
	12th	0.125	0.38	0.72	1.10	0.45	3.0	5.8	8.8	3.6
	25th	0.057	0.52	1.24	1.76	0.81	9.1	21.8	30.9	14.2*
	35th	0.095	0.42	0.63	1.05	0.54	4.4	6.6	11.0	5.7
	41st	0.121	0.36	1.14	1.50	0.38	3.0	9.4	12.4	3.1
M. M.	12th	0.007	0.05	0.09	0.14	0.24	7.1	12.9	20.0	34.3
	21st	0.023	0.11	0.02	0.13	0.26	4.8	0.9	5.6	11.3
C. S.	1st	0.025	0.015	0.067	0.082	0.13	0.6	2.7	3.3	5.2
	9th	0.082	0.22	0.33	0.55	0.50	2.7	4.0	6.7	6.1
134	1st	0.090	0.10	0.57	0.67	0.07	1.1	6.3	7.4	0.8
	6th	0.042	0.09	0.42	0.51	0.41	2.1	10.0	12.1	9.7
	12th	0.077	0.05	0.29	0.34	0.05	0.6	3.8	4.4	0.6
S. S.	2d	0.034	0.04	0.04	0.08	0.16	1.2	1.2	2.4	4.7
	3d	0.019	0.035	0.001	0.036	0.11	1.8	0	1.8	1.6
H. S.	1st	0.011	0.15	0.82	0.97	0.23	13.6	74.5	88.1	20.9
	3d	0.022	0.09	0.66	0.75	0.27	4.1	30.0	34.1	12.3
	5th	0.036	0.10	0.14	0.24	0.32	2.8	3.9	6.7	8.9
	8th	0.033	0.03	0.50	0.53	0.32	0.9	15.1	16.0	9.7
	10th	0.021	0.04	0.28	0.32	0.18	1.9	13.3	15.2	8.6
28	1st	0.004	0.08	0.21	0.29	0.13	20.0	52.5	72.5	32.5
	5th	0.006	0.08	0	0.08	0	13.3	0	13.3	0
	9th	0.010	0.08	0.04	0.12	0	8.0	4.0	12.0	0
Average ratio							2.5	9.5	12.0	8.0

* After administration of 4 Gm. of ox bile salt.

was 24.8 and 43 on the fifteenth and the seventeenth day respectively. The results are presented as ratios obtained in cases of noncalculous disease of the biliary tract. They indicate that the ratio after the patient's recovery from the obstruction probably approximates 20.

Hepatic Bile Obtained in Cases of Calculous Cholecystitis Associated with Choledocholithiasis.—This group of 13 analyses (table 9) is pre-

sented in some detail. Repeated intermittent biliary obstruction has been shown to lead to impairment of hepatic function, with a resultant low bile acid concentration of the hepatic bile even after prolonged drainage.[4] As a result, the total bile acid-cholesterol ratio in the cases considered here was low. In some instances there was a tendency for the ratio to rise gradually after the obstruction had been released. Certain exceptions must be noted. When operation was performed immediately during an acute obstruction (case of H. S. and case 28), the drainage bile during the first few days gave a very high ratio (88.1 for H. S. and 72.5 in case 28), apparently as a result of hepatic injury due to acute back pressure on the liver. One other point may be noted. In the case of S. M., after the administration of 4 Gm. of ox bile salts the total bile acid-cholesterol ratio rose from 8.12 to 30.9.

TABLE 10.—*Hepatic Bile Obtained in a Case of Stricture of Choledochus Eight Months After Operation (Case T. R.)*

Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
1st	0.037	0.05	0.05	0.10	0.10	1.3	1.3	2.7	2.7
3d	0.022	0.06	0.14	0.20	0.80	2.7	6.4	9.1	36.4
4th	0.059	0.08	0.17	0.25	0.94	2.0	4.4	6.4	2.4
5th	0.034	0.09	0.24	0.33	0.29	2.6	7.1	9.7	8.5
7th	0.030	0.08	0.32	0.40	0.17	2.7	10.7	13.3	5.7
9th	0.077	0.12	0.55	0.67	0.27	1.6	7.1	8.7	2.5
16th	0.100	0.08	1.23	1.31	0.37	0.8	12.3	13.1	1.7

Hepatic Bile Obtained in Cases of Stricture of the Choledochus.—A patient (T. R., table 10) had an almost complete obstruction of the choledochus for eight months as a result of a stricture following a primary cholecystectomy. The analyses revealed the excretion of the different bile acids to be in abnormal proportions. The predominant features were: (1) almost total absence of cholic acid, (2) a high proportion of desoxycholic acid and (3) a low concentration of conjugated bile acids. As can be seen, the total bile acid-cholesterol ratio was 2.7 on the first day, but thereafter it showed an average of about 10.

Hepatic Bile Obtained in Cases of Acute Pancreatitis.—The results of analysis of bile in 3 cases of acute pancreatitis are presented in table 11. In each instance the total bile acid concentration after about the eighth day tended to be much higher than in the previously presented cases of choledocholithiasis (table 9). The cholesterol concentration, however, also tended to be high. As a result the total bile acid-cholesterol ratio was rather low, except in the drainage bile on the twelfth day in case 62.

TABLE 11.—*Hepatic Bile Obtained in Cases of Acute Pancreatitis*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
G. K.	2d	0.055	0.07	0.08	0.15	0.26	1.2	1.4	2.6	4.7
	3d	0.032	0.04	0.05	0.09	0.13	1.2	1.6	2.8	4.1
	4th	0.041	0.07	0.01	0.08	0.26	1.7	0.2	1.9	6.3
	5th	0.079	0.30	0.50	0.80	1.12	3.3	6.3	9.6	14.2
	8th	0.176	0.50	0.82	1.32	1.05	2.9	4.6	7.5	6.0
	10th	0.147	0.39	0.85	1.24	1.06	2.0	5.8	7.8	7.7
S. Z.	1st	0.230	0.43	0.28	0.71	0.80	1.9	1.2	3.1	3.5
	2d	0.253	0.20	0.04	0.24	0.49	0.8	0.2	1.0	1.9
	3d	0.252	0.27	0.12	0.39	0.68	1.1	0.5	1.6	2.7
	4th	0.140	0.53	0.19	0.72	0.95	3.8	1.3	5.1	6.8
	6th	0.115	0.28	0.12	0.40	0.79	2.4	1.0	3.4	6.8
	12th	0.118	0.54	0.64	1.18	0.94	4.6	5.4	10.0	8.0
	19th	0.127	0.54	0.39	0.96	1.01	4.3	3.1	7.2	8.0
62	2d	0.038	0.26	0.11	0.37	....	6.8	2.9	9.7	...
	5th	0.048	0.23	0.29	0.52	....	4.8	6.0	10.8	...
	12th	0.061	0.77	0.56	1.35	0.78	12.6	9.2	21.8	12.8

TABLE 12.—*Hepatic Bile Obtained in Cases of Hepatitis and Cholangitis*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio				Comment
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	
F. F.	1st } 2d }	0.002	0.45	0.10	0.55	0.65	225.0	50.0	275.0	325.0	Long history of epigastric pain; pruritus; jaundice; acute interstitial hepatitis
	3d	0.089	0.17	0.06	0.23	0.08	1.9	0.6	2.6	0.8	
	5th	0.033	0.04	0.05	0.09	0.08	1.2	1.5	2.7	2.6	
	7th	0.003	0	0	0	0.27	0	0	0	90.0	
	9th	0.003	0.11	0.12	0.23	0.21	36.7	40.0	76.7	70.0	
	10th	0.002	0.13	0.38	0.51	0.32	65.0	190.0	255.0	160.0	
133	4th	0.003	0.07	0.07	0.14	0.03	23.3	23.3	46.6	10.0	Jaundice; pruritus; swollen liver; narrowed biliary tree; serous hepatitis (?)
	12th	0.004	0.06	0.10	0.16	0.16	15.0	25.0	40.0	40.0	
	19th	0.005	0.07	0.08	0.15	0.11	14.0	16.0	30.0	22.0	
	26th	0.006	0.06	0.10	0.16	0.35	10.0	16.6	26.6	58.3	
	34th	0.022	0.14	0.33	0.47	0.27	6.4	15.0	21.4	12.3	
	41st	0.021	0.06	0.13	0.19	0.26	2.9	6.2	9.1	12.3	
C. S.	2d	0.002	0	0.04	0.04	0	0	20.0	20.0	0	Acute cholangitis; pyelophlebitis; Diabetes
	3d	0.003	0	0.23	0.23	0	0	76.7	76.7	0	
	4th	0.005	0	0.04	0.04	0	0	8.0	8.0	0	
S. C.	1st } 3d }	0.015	0.06	0.15	0.21	0.36	4.0	10.0	14.0	24.0	Acute cholangitis; parenchymatous degeneration
	8th	0.013	0.01	0.03	0.04	0.10	0.77	2.3	3.1	7.7	
J. K.	1st	0.083	0.25	0.69	0.94	0.54	3.0	8.3	11.3	6.5	Marked jaundice and pruritus 12 years after cholecystectomy; chronic cholangitis; partial obstruction due to angulation of the drainage tube after the 80th day
	12th	0.046	0.08	0.18	0.26	0.33	1.7	3.9	5.6	7.2	
	16th	0.032	0.12	0.23	0.35	3.75	7.2	10.9	18.1	117.2	
	21st	0.024	0.17	0.26	0.43	0.29	7.1	10.8	17.9	12.1	
	26th	0.025	0.21	0.39	0.60	0.56	8.4	15.6	24.0	22.4	
	37th	0.020	0.28	0.31	0.59	0.62	14.0	15.5	29.5	31.0	
	48th	0.039	0.37	0.33	0.70	0.92	9.5	8.5	17.9	23.6	
	81st	0.006	0.11	1.09	1.20	0.71	18.3	181.7	200.0	118.3	
	88th	0.026	1.01	0.41	1.42	1.17	38.8	15.8	54.6	45.0	
	94th	0.055	0.30	0.06	0.36	0.58	5.4	1.1	6.5	10.5	
I. R.	8th	0.032	0	0.10	0.10	0	0	3.1	3.1	0	Acute hepatitis; edematous bile ducts and gallbladder; cholecystostomy
	12th	0.037	0.02	0.05	0.07	0.21	0.5	1.3	1.8	5.7	
E. S.	1st	0.006	0.04	0.16	0.20	0.08	6.7	26.7	33.3	13.3	Chronic cholecystitis and cholangitis; choledocholithiasis
	3d	0.017	0.04	0.31	0.35	0.22	2.3	18.2	20.6	12.9	
	10th	0.014	0.07	0.25	0.32	0.17	5.0	17.9	22.9	12.1	
F. J.	2d	0.053	0.05	0.07	0.12	0.17	0.9	1.3	2.3	3.2	Acute cholangitis; early carcinoma of right hepatic duct
	3d	0.023	0.02	0.24	0.26	0.09	0.9	1.7	2.6	3.9	
	4th	0.019	0.025	0.026	0.051	0.13	1.3	1.4	2.7	6.8	
	5th	0.023	0.04	0.02	0.06	0.21	1.7	0.9	2.6	9.3	
	7th	0.062	0.10	0.21	0.31	0.38	1.6	3.4	5.0	6.1	
	9th	0.047	0.13	0.36	0.49	0.51	2.8	7.7	10.4	10.8	
	13th	0.076	0.14	0.37	0.51	0.46	1.8	4.9	6.7	6.0	
	15th	0.079	0.17	0.18	0.35	1.07	2.2	2.3	4.4	13.6	
	35th	0.050	0.42	0.05	0.47	1.03	8.4	1.0	9.4	20.6	
	108th	0.085	0.29	0.29	0.58	1.19	3.4	3.4	6.8	14.0	

Hepatic Bile Obtained in Cases of Hepatitis and Cholangitis.—The analyses of hepatic bile made in 8 cases show the effect of injury to the liver on the excretion of cholesterol (table 12). The data can be correlated with the results of analyses of gallbladder bile obtained in cases of similar conditions (table 7). The high total bile acid-cholesterol ratio is especially to be noted in drainage bile obtained during the first few days in cases of hepatitis. In the case of F. F. the first two days' drainage gave a ratio of 275; in case 133 the ratio was 46.6 on the fourth day, and in the case of C. S. the ratio was 76.7 on the third day.

TABLE 13.—*Bile Obtained After Administration of Bile Salts in a Case of Complete Fistula Following Carcinoma of the Pancreas (case 23)*

		Bile Acid Percentage				Bile Acid-Cholesterol Ratio				
Date	Cholesterol, %	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Bile Acid Administered
Sept. 17	0.150	0.38	0.74	1.12	0.81	2.5	4.9	7.4	5.4	
18	0.129	0.47	0.61	1.08	0.96	3.6	4.7	8.3	7.5	
19	0.206	0.36	0.75	1.11	1.03	1.7	3.6	5.3	5.0	
20	0.173	0.25	1.19	1.44	1.42	1.4	6.9	8.3	8.2	15 Gm. desoxycholic
21	0.172	0.24	1.24	1.48	1.45	1.4	7.2	8.6	8.3	10 Gm. desoxycholic
22	0.121	0.13	1.66	1.79	1.82	1.1	13.7	14.8	15.0	15 Gm. desoxycholic
23	0.137	0.13	1.31	1.44	1.00	0.9	9.6	10.5	7.3	
24	0.128	0.70	0.38	1.08	0.92	5.5	3.0	8.5	7.2	
25	0.099	1.05	0.31	1.36	1.17	10.6	3.1	13.7	11.8	15 Gm. cholic
26	0.077	0.89	0.62	1.51	1.28	11.5	8.0	19.5	16.6	15 Gm. cholic
27	0.097	0.95	1.37	2.32	1.28	9.8	14.1	23.9	13.2	15 Gm. cholic
28	0.112	0.95	1.13	2.18	1.11	8.5	10.1	18.6	10.0	
29	0.123	1.11	1.72	2.83	1.06	9.0	14.0	23.0	8.6	
30	0.112	1.07	1.34	2.41	0.95	9.6	11.0	20.6	8.5	
Oct. 1	0.149	0.71	0.44	1.15	0.56	4.8	3.0	7.8	3.8	
2	0.128	0.45	0.51	0.96	0.59	3.5	4.0	7.5	4.6	

In cases of chronic and acute cholangitis the total bile acid-cholesterol ratio tends to be rather low (cases of J. K. and F. J.). When both cholangitis and hepatic degeneration were found, the ratio tended to be low (case S. C.). On the other hand, when acute obstruction was associated with cholangitis (as in the case of J. K. after the eightieth day of drainage, and in the case of E. S.), the ratio was high. In 1 case (that of I. R.) bile drained through an edematous and inflamed gallbladder. As a result, a large proportion of the bile acids was absorbed, apparently much more rapidly than the cholesterol. This resulted in a very low total bile acid-cholesterol ratio.

Bile Obtained to Determine the Effect of Administration of Bile Salts.—In the case of S. M. (table 9) it was noted that the total bile acid-cholesterol ratio was raised following the administration of 4 Gm. of ox bile salts. Similar effects were produced in 2 other cases reported here. In case 23 (table 13) large amounts of desoxycholic acid and

also of cholic acid were administered. The patient had a choledochal fistula as a result of obstruction due to carcinoma of the pancreas. The bile was reinjected daily by means of a small stomach tube. After the administration of desoxycholic acid the bile acid concentration rose. As a result, the bile acid-cholesterol ratio was raised. After the administration of cholic acid the cholesterol percentage rose somewhat, but the amount of total bile acids rose noticeably. As a result, the ratio was elevated during the period of administration of cholic acid. Sim-

TABLE 14.—*Bile Obtained After Administration of Bile Salts in a Case of Cholangitis and Carcinoma of the Right Hepatic Duct (Case of F. J.)*

Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Ox Bile Salts Administered, Gm.
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	
Second operation										
10th	0.007	0.01	0.32	0.33	0.04	1.4	45.7	47.1	5.7	4
20th	0.011	0.03	0.36	0.39	0.85	2.7	32.7	35.5	77.3	4
36th	0.013	0.03	0.09	0.12	0.27	2.3	6.9	9.2	20.8	
40th	0.011	0.02	0.31	0.33	0.25	1.8	28.2	30.0	22.7	4
42d	0.012	0.007	0.024	0.031	0.32	0.6	2.0	2.6	26.7	
44th	0.007	0.04	0.26	0.20	0.22	5.7	37.1	42.9	31.4	5
45th	0.003	0.07	0.46	0.53	0.05	23.3	153.3	176.7	16.7	5
46th	0.015	0.08	0.12	0.20	0.03	5.3	8.0	13.3	2.0	
47th	0.014	0.12	0.08	0.20	0.05	8.6	5.7	14.3	3.6	4
48th	0.012	0.09	0.14	0.23	0.02	7.5	11.5	19.2	1.7	1.3
49th	0.025	0.09	0.08	0.17	0	1.3	1.2	6.8	0	
51st	0.015	0.09	0.04	0.13	0.27	6.0	2.7	8.7	18.0	
52d	0.012	0.016	0.032	0.048	0.29	1.3	2.7	4.0	24.2	5
57th	0.032	0.07	0.78	0.85	0.20	2.2	24.4	26.6	6.2	5
58th	0.017	0.09	0.63	0.72	0.28	5.3	37.1	42.0	16.5	5
63d	0.021	0.07	0.52	0.59	0.10	3.3	24.8	28.1	4.8	5
65th	0.032	0.13	0.36	0.49	0.33	4.1	11.2	15.0	10.3	5
69th	0.026	0.11	0.60	0.71	0.38	4.2	23.1	27.3	14.6	5
74th	0.034	0.11	0.32	0.43	0.34	3.2	9.4	12.6	10.0	5
78th	0.024	0.15	0.51	0.66	0.49	6.2	21.3	27.5	20.4	5
84th	0.021	0.15	0.45	0.60	0.41	7.1	21.4	28.1	14.8	5
90th	0.020	0.17	0.42	0.59	0.23	8.5	21.0	29.5	11.5	5
95th	0.034	0.12	0.51	0.63	0.44	3.5	15.0	18.5	12.9	5
97th	0.033	0.19	0.61	0.80	0.57	5.8	18.5	24.2	16.7	5
112th	0.019	0.01	0.21	0.22	0.20	0.5	11.1	11.6	10.5	
115th	0.025	0.01	0.12	0.13	0.14	0.4	4.8	5.2	5.6	
147th	0.029	0.07	0.46	0.53	0.32	2.4	15.9	18.3	11.0	2
156th	0.033	0.12	0.53	0.65	0.26	3.6	16.1	19.7	7.9	2
184th	0.019	0.07	0.66	0.73	0.39	3.7	34.7	38.4	20.5	2
191st	0.013	0.04	0.28	0.32	0.22	3.1	21.5	24.6	16.9	2

ilar results were produced in a case of long-continued fistula resulting from the presence of cholangitis and a carcinoma of the right side of the liver (table 14). With each cessation of administration of bile salts, the ratio fell. Ox bile salts were administered in this case.

Bile Obtained to Determine the Effect of Various Diets.—An attempt was made to determine the influence of diet on the total bile acid-cholesterol ratio. In the case of a patient (M. F., table 15) who had been operated on for calculous cholecystitis and choledocholithiasis, an attempt was made to feed pure carbohydrate, pure protein and pure fat diets. Although these diets were somewhat disagreeable, the patient

took them for three day periods after he had completely recovered from the operation. Bile was collected over twenty-four hour periods, and equal quantities were pooled for three day periods. There was a daily loss of 300 to 500 cc. of bile through the fistula, but the loss of bile salts was partially made up by giving the patient 3 Gm. of ox bile salts every day. During the experimental period the cholesterol concentration gradually rose, but at the same time the bile acid concentration also rose, so that the total bile acid-cholesterol ratio did not vary with the different diets. The cholesterol concentration was highest during and after the taking of the fat diet, but the results, although suggestive, cannot be considered significant. It is of interest to note that after the

TABLE 15.—*Bile Obtained to Test the Effect of Various Diets on the Bile Acid–Cholesterol Ratio (Case of M. F.: Calculous Cholecystitis, Choledocholithiasis)*

Day After Operation	Cholesterol, %	Bile Acid Percentage			Bile Acid–Cholesterol Ratio			Diet for 3 Day Periods
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	
20th.....	0.043	0.19	0.25	0.44	4.4	6.0	10.4	Hospital diet
22d, 23d, 24th..	0.073	0.21	0.18	0.39	3.0	2.5	5.5	High carbohydrate CHO, 700; P, 48; F, 3
25th, 26th, 27th	0.059	0.20	0.12	0.32	3.4	2.0	5.4	High protein CHO, 96; P, 244; F, 77
28th, 29th, 30th	0.111	0.36	0.27	0.63	3.2	2.4	5.6	High fat CHO, 18; P, 43; F, 300
31st, 32d, 33d...	0.148	0.55	0.27	0.82	3.7	1.8	5.5	Hospital diet
34th, 35th.....	0.121	0.38	0.31	0.69	3.1	2.5	5.6	Hospital diet
40th.....	0.095	0.56	0.40	0.96	5.9	4.1	10.0	Hospital diet; drainage after closure of tube for 5 days

fistula tube had been closed for five days, thus establishing a closed enterohepatic circulation of bile salts, the ratio rose to 10, and the bile acid concentration, although somewhat low, reached its highest point.

Canine Gallbladder and Hepatic Bile.—Since a great deal of investigative work has been done on canine bile, three tables are presented on the results of analyses of gallbladder bile and hepatic bile. Table 16 summarizes the results of 8 analyses of gallbladder bile. The average ratio was found to be 161 for cholic acid, 246 for total bile acids, and 135 for conjugated bile acids. Table 17 summarizes the results of analyses made during experiments on a dog with a McMaster fistula to which the bile was refed. The fistula was obstructed for a five day period and a ten day period by clamping the drainage tube. As can be seen, the total bile acid concentration tended to drop gradually after each period of obstruction. The cholesterol concentration tended to be

little influenced except immediately following the operation and immediately after the release of acute obstruction, when the cholesterol concentration was very low. As in the human being, the total bile salt-

TABLE 16.—*Gallbladder Bile from Dogs*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
65	0.108	7.31	6.01	13.32	8.56	68	56	123	79
74	0.072	8.48	3.30	11.78	10.75	118	46	164	135
X	0.055	11.94	2.30	14.24	7.81	217	42	259	142
P	0.054	4.28	6.18	10.46	4.14	79	114	194	77
79	0.054	9.97	8.50	18.47	9.04	185	157	342	167
76	0.080	9.14	8.83	17.97	7.58	114	110	225	95
31	0.055	10.67	5.29	15.96	7.39	194	96	290	134
75	0.033	10.37	2.12	12.49	8.18	314	64	378	248
Average	64	9.02	5.32	14.34	7.93	161	85	246	135

TABLE 17.—*Bile from Dog with Biliary Fistula; Bile Refed*

Dog 67: Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid–Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
2d	0.004	0.8	0.7	1.6	2.0	190	215	405	490
5th	0.008	1.5	2.4	3.9	2.9	184	304	488	360
7th	0.013	2.7	1.6	4.3	3.4	207	125	331	263
12th	0.011	2.7	1.9	4.6	3.0	243	173	416	274
12th to 17th day, obstruction									
19th	0.007	1.1	1.3	2.4	1.0	154	189	343	137
20th	0.014	1.7	1.7	3.0	1.8	123	94	216	126
21st	0.020	2.1	2.2	4.2	2.9	103	108	211	146
23d	0.016	2.0	1.7	3.7	1.8	125	106	231	100
26th	0.014	1.6	1.1	2.7	1.9	117	77	194	137
28th	0.013	1.6	1.0	2.6	1.7	124	83	207	134
28th to 38th day, obstruction									
40th	0.006	1.1	1.8	2.9	1.3	188	293	482	213
42d	0.007	1.8	0.8	2.6	2.2	263	114	377	316
44th	0.014	1.6	1.3	2.9	1.9	117	90	207	136
47th	0.009	1.4	0.7	2.2	1.5	161	80	241	172
49th	0.008	1.8	0.5	2.2	1.8	222	50	281	227
51st	0.006	0.9	1.3	1.0	1.4	143	225	368	225
53th	0.005	1.0	0.2	1.2	1.4	202	40	242	280
57th	0.006	1.4	0.7	2.1	1.6	232	120	352	263
59th	0.008	1.6	0.6	2.3	1.9	204	79	283	239
62d	0.011	1.7	0.3	2.1	1.8	159	29	188	264
64th	0.004	0.8	0	0.8	0.8	202	5	207	197
Average		1.5	1.1	2.6	1.9	174	125	298	218

cholesterol ratio was accordingly increased at these periods. The cholesterol concentration was so low and the variations so small that the figures cannot be considered significant.

Table 18 summarizes the results of feeding large quantities of various pure bile acids to a dog with a McMaster fistula. No bile was

refed. The results are similar to those in the human being in that the concentration of cholesterol was not significantly influenced by increasing the concentration of bile acids in the bile as a result of their administration. Consequently the total bile acid-cholesterol ratio tended to be definitely increased each time bile salts were administered. It is to be noted that only a trace of cholesterol was present in the bile after the administration of dehydrocholic acid. This result may have been due to the fact that cholesterol is insoluble in dehydrocholic acid.

TABLE 18.—*Bile Obtained After Administration of Bile Salts to Dog with McMaster Fistula*

Dog 79:		Bile Acid Percentage				Bile Acid–Cholesterol Ratio				
Day After Operation	Cholesterol, %	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Comment; Bile Acid Administration
4th	0.004	0.62	0.28	0.90	0.65	155	70	225	162	
8th	0.012	1.50	0.40	1.90	1.28	125	33	158	107	
12th	0.013	1.82	1.31	3.13	0.68	140	100	240	52	4 Gm. cholic (3 days)
16th	0.012	1.10	0.89	1.99	0.56	91	74	165	47	
20th	0.007	0.34	1.39	1.73	0.48	49	198	247	68	4 Gm. desoxycholic (3 days)
24th	0.006	0.56	1.14	1.70	0.30	93	190	283	50	
26th	0.008	0.36	1.75	2.11	0.30	45	218	253	37	8 Gm. desoxycholic (2 days)
27th	0.010	1.01	1.72	2.73	0.98	101	172	273	98	
29th	0.010	1.34	1.65	2.99	0.35	134	165	299	35	8 Gm. cholic (2 days)
31st	0.009	0.93	1.03	1.96	0.87	103	114	217	97	
33d	0.011	1.64	1.91	3.55	1.50	149	173	322	136	8 Gm. ox bile salts (2 days)
34th	0.008	0.94	0.84	1.78	0.94	117	105	222	117	
36th	0.012	1.90	1.80	3.70	1.70	158	150	308	142	8 Gm. ox bile salts (2 days)
38th	0.015	1.50	1.90	3.40	1.23	100	126	226	82	
40th	0.012	1.90	1.52	3.42	1.90	158	126	285	158	8 Gm. glycocholic (2 days)
45th	0.011	1.05	1.33	2.38	0.66	95	120	216	60	
47th	0.012	1.76	1.51	3.27	1.39	147	125	272	115	8 Gm. glycocholic (2 days)
49th	0.009	1.19	0.97	2.16	0.88	132	107	240	98	
51st	0.008	0.37	1.60	1.97	0.89	46	200	246	111	8 Gm. desoxycholic (2 days)
53d	0.004	0.58	0.41	0.99	0.56	145	102	247	140	
55th	0.001	0.22	0.71*	0.93	0.20	220	710*	930	200	6 Gm. dehydrocholic (2 days)
56th	0.001	0.33	0.50*	0.83	0.52	330	500*	830	520	

* Dehydrocholic acid (?).

COMMENT

The data on gallbladder bile obtained from normal gallbladders and in cases of carcinoma of the pancreas as well as from hepatic drainage after the tenth day following the operation suggest that the normal total bile acid-cholesterol ratio in human bile lies somewhere around 20. In cases of early chronic cholecystitis the total bile acid-cholesterol ratio was found to average 13. With more advanced cholecystitis the ratio fell to 7.7 and when acute cholecystitis was present the ratio was 6. The

ratios were of course much higher than those obtained by the Gregory-Pascoe (cholic acid) method, and they were somewhat higher than the ratios calculated from the results of the Schmidt-Dart method for bile acids (conjugated bile acids). Why was the bile acid-cholesterol ratio lowered? May it be inferred that the damaged gallbladder absorbed the bile acids more rapidly than the cholesterol and that this resulted in the lowering of the ratio? That such a course of events takes place with acute cholecystitis is strongly suggested both by previous experimental work [6] and by a comparison of the analyses presented here of the bile obtained from the two groups of chronically diseased functioning gallbladders (table 3) and of that obtained from acutely inflamed gallbladders (table 5). The average cholesterol concentration was almost exactly similar in the two groups (0.540 per cent and 0.546 per cent). The second group contained chronically diseased gallbladders which had become suddenly inflamed. Since the cholesterol concentrations were equal in the two groups, may we not infer that the bile acid concentrations were also similar just prior to the onset of inflammation and that the low bile acid content in the cases of acute inflammation was due to absorption of the acids?

However, another possible reason for the low bile acid-cholesterol ratio may be considered. The analyses of hepatic bile obtained in cases of chronic cholecystitis associated with choledocholithiasis indicate that the liver often secretes a rather low concentration of bile acids. The cholesterol concentration tends to be relatively high, however, and seems to be only partially influenced by the bile acid concentration. The gradually rising bile acid-cholesterol ratio after an operation seems to be due, in great part, to the increasing concentration in bile acids. The excretion of cholesterol tends to be fixed, although it is influenced to some extent by physical factors of solubility. The figures, then, suggest that the low bile acid-cholesterol ratio associated with chronic cholecystitis may possibly be due not to absorption of bile acids by the diseased gallbladder wall but to a diminished excretion of bile acids by the liver.

The bile acid-cholesterol ratio can be considered of importance only if the type of bile acid present is known. Cholesterol is about four times as soluble in a 3 per cent solution of sodium desoxycholate as in a solution of cholate. The saturation point of and the precipitation of cholesterol from bile will be determined by the type of bile acid present. According to Spanner and Bauman,[5] cholesterol (theoretically) will precipitate in cholic acid if the ratio falls below 80, while it will not precipitate in a desoxycholate solution until the ratio is below 20. Actually, in addition to the factor of simple solubility, cholesterol forms addition compounds with desoxycholic acid.[6] If a bile salt solution is shaken up with finely ground cholesterol for four hours and then care-

fully filtered, the desoxycholate-cholesterol ratio, 20, will be similar to that found by Spanner and Bauman [5] in a 3 per cent solution, and slightly lower in more concentrated solutions (table 19). If, however, sodium desoxycholate is dissolved in alcohol and excess cholesterol is added, addition compounds are formed. If this solution is dried, the residue redissolved in water and the excess cholesterol filtered off, the desoxycholate-cholesterol ratio will be found to be about 10. In other words, the danger of precipitation of cholesterol is no greater in a 1:80 solution of cholesterol in sodium cholate than in a 1:10 solution of cholesterol in sodium desoxycholate. In previous presentations [4] it was shown that with increasing degrees of cholecystitis the ratio of cholic acid to desoxycholic acid in the bile fell. Similar low ratios of cholic to desoxycholic acid were found in chronic cholangitis and also in prolonged intermittent biliary obstruction. It therefore follows that the total bile acid-cholesterol ratio is no indication of the degree of satura-

TABLE 19.—*Solubility of Cholesterol in Sodium Desoxycholate*

Percentage of Desoxycholate	Cholesterol Held in Solution After Mechanical Shaking		Cholesterol Held in Solution After Forming Addition Compound in Alcohol	
	Percentage	Ratio	Percentage	Ratio
2.0	0.085	23.5	0.156	12.8
4.0	0.240	16.6	0.400	10.0
8.0	0.476	16.8	0.770	10.4

tion of cholesterol in any one sample of bile. Since the amount of desoxycholic acid is relatively increased, a total bile acid-cholesterol ratio of 10 in bile from a patient with chronic cholecystitis may indicate a cholesterol saturation no greater than does a ratio of 20 in normal bile.

As a matter of fact, there are still unknown factors which keep cholesterol in solution in bile. The presence of phosphatides and of neutral fats and fatty acids in bile may exert a considerable influence in keeping cholesterol in solution. This is especially true of bile in which the bile acid concentration is very low. In such bile there may be a bile acid-cholesterol ratio as low as 1 (table 9).

The very high total bile acid-cholesterol ratio found in both the gallbladder bile and the hepatic bile of patients with hepatitis and with acute obstruction of the liver supports the conception, suggested by Wright and Whipple,[10a] that the excretion of cholesterol in bile is a

10. (*a*) Wright, A., and Whipple, G. H.: Bile Cholesterol: Fluctuations Due to Diet Factors, Bile Salt, Liver Injury, and Hemolysis, J. Exper. Med. **59**:407, 1934. (*b*) McMaster, P. D.: Studies on Total Bile, ibid. **40**:25, 1924. (*c*) Dostal, L. E., and Andrews, E.: Etiology of Gall Stones: III. Effect of Diet on the Bile Salt-Cholesterol Ratio, Arch. Surg. **26**:258 (Feb.) 1933. (*d*) Bac-

function of the hepatic parenchyma independent of bile acid excretion. After acute injury to the liver it is evident that the excretion of cholesterol practically ceases while the percentage of bile acids excreted, although reduced, is still considerable. The relatively unchanged concentration of cholesterol in continued hepatic drainage, in spite of fluctuations in bile acid concentration, further supports the conception of a relatively independent cholesterol function of the liver cells. Similarly, the oral administration of bile salts, both to man and to the dog, has little influence on the concentration of cholesterol excreted by the liver, although desoxycholic acid seems to have a slight tendency to increase the cholesterol concentration.

If the excretion of cholesterol is dependent on some function of the liver cells which is reduced by acute injury, may it not be concluded that the rather high excretion of cholesterol in cases of disease of the gallbladder is due to hyperfunction of the hepatic cell? Such speculations raise questions as to the factors which influence the excretion of cholesterol by the liver. Within the limits of the physical factor of solubility, the excretion of bile acid has little influence on the excretion of cholesterol. It is known, however, that cholesterol metabolism is bound up in some way with lipoid metabolism. Gallstones are more common in stout persons, who increase their fat depots readily and for whom reduction of weight is very difficult. Excretion of biliary cholesterol is greatest during starvation,[10b, c] when the metabolism of fats is greatly increased. In acute pancreatitis there seems to be a somewhat increased excretion of biliary cholesterol (table 11). Bacmeister [10d] found evidence of increased biliary excretion of cholesterol by persons with diabetes in whom metabolism of fats is encouraged by a high fat diet. However, Dostal and Andrews [10e] were not able to confirm this. Experimental work on both dogs and human beings indicated that the administration of a high fat diet has no influence on the biliary excretion of cholesterol.[10a, c]. Our own experiments on a human being (table 15) indicate that a prolonged high intake of fat has a tendency to raise the biliary excretion of cholesterol. It must be remembered that the biliary excretion of cholesterol in man, as compared with that in other species, is exceptionally high. The only other species studied that has a high bile cholesterol concentration is the pig, whose predisposition to deposit fat, if not abnormal, is certainly exceptional.

The points presented here are brought out to emphasize that further investigation should be directed not to the bile acid-cholesterol ratio but to the factors, probably associated with lipoid metabolism, which

meister: Untersuchungen über Cholesteril Ausscheidung in menschlichen Gallen, Biochem. Ztschr. **26**:223, 1910. (*e*) Fox, F. W.: The Composition of Human Bile and Its Bearing upon Sterol Metabolsim, Quart. J. Med. **21**:107, 1927.

modify the excretion of bile cholesterol. The evidence recently presented by Dragstedt [11] that the pancreas secretes a hormone which is involved in the metabolism of fat is suggestive of a possible mode of attack on the problem.

If cholesterol tends to precipitate in bile in which the bile acid-cholesterol ratio is lowered, our evidence indicates that the ratio may be readily raised by the oral administration of bile salts. It is raised especially after the administration of cholic acid or of ox bile salts, which contain a high percentage of cholic acid. This seems to be due to the fact that in man the administration of cholic acid is more effective than the administration of desoxycholic acid in raising the concentration of bile acids in hepatic bile.[12]

CONCLUSIONS

The normal total bile acid-cholesterol ratio in human bile as determined in our studies was about 20. In cases of early chronic cholecystitis the ratio averaged 13, while in cases of advanced chronic cholecystitis the ratio averaged 7.7. The danger of the precipitation of cholesterol is only slightly increased, since the relative amount of the most effective solvent, desoxycholic acid, is greatly increased. In cases of acute cholecystitis the average total bile acid-cholesterol ratio was 6. The high cholesterol concentration increases the possibility of precipitation out of solution.

If the liver is injured, as in hepatitis, in inflammation or in acute obstruction, the excretion of cholesterol is much more markedly reduced than is the excretion of bile acids.

Evidence is presented which suggests that the excretion of biliary cholesterol is controlled by some independent function of the hepatic cell, which is related to lipoid metabolism.

The bile acid-cholesterol ratio is readily raised by the oral administration of large amounts of bile salts, especially cholate. This may diminish the danger of the precipitation of cholesterol from the bile.

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REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomaly.—Braasch and Merricks [1] reported a series of 27 cases of proved renal agenesia observed at the Mayo Clinic from 1909 to the present time. The diagnosis was established at operation in 14 cases and at necropsy in 13 cases. In another series of 42 cases, the diagnosis was inferred from roentgenographic and cystoscopic data. This makes a total of 69 cases.

The most frequent subjective symptom was pain on the side on which the kidney was present, which occurred in 38 of the 69 cases. The pain was usually dull, although in 8 cases it was rather severe.

Findings at physical examination were normal in 46, or 66 per cent, of the 69 cases. In the 23 cases in which abnormal conditions were observed, the presence of a palpable mass in the flank on the side on which the kidney was present was the most frequent finding; it occurred in 17, or 24 per cent, of the total number of cases. The next most fre-

1. Braasch, W. F., and Merricks, J. W.: Clinical and Radiologic Data Associated with Congenital and Acquired Single Kidney, Tr. Am. A. Genito-Urin. Surgeons **30**:103-112, 1937.

quent finding was tenderness to palpation on the side on which the kidney was present; this occurred in 11 cases, or 16 per cent.

Cystoscopic observation of the trigon often will reveal signs suggestive of renal agenesia. Hypertrophy of the interureteral ridge on the side on which the kidney is present usually is well defined, and there is complete absence of the ridge on the other side. Compensatory hypertrophy of the ureteral orifice is usually evident, and urinary expulsion at this point is as a rule more energetic and frequent.

The average size of the normal kidney as measured by means of 100 consecutive excretory urograms was 12 by 6 cm. In 24 cases of renal agenesia the average size of the male kidney was 15.7 by 8.1 cm. and that of the female kidney was 14.8 by 7.1 cm. Thus, the long axis of the kidney averaged 0.9 cm. more for men than for women, and the width for men was 1 cm. greater than for women.

Measurements of the acquired solitary kidney were made with roentgenograms taken in 31 cases observed during the last six months. The average renal outline measured 14.7 by 7.1 cm. In the 8 instances in which the patients were women the average size was 14.6 by 6.6 cm. In the 23 instances in which the patients were men the average size was 14.7 by 7.2 cm. Thus, the chief difference was in the width of the renal outline. The degree of hypertrophy of the acquired single kidney is distinctly less than in cases of renal agenesia. These findings negate the opinion held by some surgeons that if a kidney on exploration is found to be normal and not hypertrophied there must be a functioning kidney on the other side.

There is a relative increase in size of the renal pelvis, which does not equal that of the parenchyma. Little difference in the size of the renal pelvis exists in cases of congenital or acquired single kidney. The renal outline generally is situated lower in cases of renal agenesia than in cases of acquired single kidney or normal kidney. This may be regarded as a definite factor in differential diagnosis. The outline of the psoas muscle is less sharply defined on the side on which the kidney is absent in urograms taken in cases of congenital and acquired single kidney than in an unselected series of urograms. In a few cases of agenesia there is an increase in the width of the psoas muscle on the side on which the kidney is absent.

Beer and Ferber [2] reported a series of cases of crossed renal ectopia (unilateral, fused or elongated kidney). Their report is in agreement with others previously published in that the left kidney was crossed more

2. Beer, E., and Ferber, W. L. F.: Crossed Renal Ectopia (Unilateral, Fused or Elongated Kidney), with Report of Fourteen Cases Clinically Diagnosed and Two Cases Encountered at Autopsy During the Past Eighteen Years, J. Urol. **38**:541-561 (Dec.) 1937.

often than the right (9 cases as compared with 7). Also, more of the patients were men than were women (12 patients as compared with 4, respectively). They have noted an autopsic incidence considerably higher than is indicated by the reports of others (condition observed twice in a series of 7,400 autopsies). They have observed the presence of a mass in 9 cases, an important factor in directing attention to the possible presence of this condition. Pain was the outstanding symptom, occurring 8 times. In 5 cases there were no symptoms. In 13 cases the correct diagnosis was made by roentgenologic examination after the presence of some anomalous renal condition had been suspected during the course of ventral suspension of the uterus. The condition in 2 cases was discovered at necropsy. They observed 2 cases in which the kidneys were unfused. This is an incidence of 13.5 per cent, which is consistent with Pagel's figure. Their series presented a rather high incidence of pathologic involvement (66.6 per cent). The prime complication was hydronephrosis. Calculus was present in 3 cases. An operative procedure was performed in 3 instances after a correct preoperative diagnosis had been made.

Beer and Ferber [2] concluded that the diagnosis of crossed ectopic kidney never will be missed if opaque ureteral catheters are employed in every instance. In the future this condition unquestionably will be discovered oftener by means of excretory urograms. The presence of a unilateral mass resembling an enlarged kidney in shape should arouse suspicion of the possible existence of crossed renal ectopia. The anomalous position of the pelvis, the ureter and the vessels accounts for the relatively high incidence of obstructive hydronephrosis. When conditions requiring surgical intervention exist within either kidney the necessary procedure can be performed without hesitancy after the true anatomic arrangement has been determined preoperatively.

Mackenzie and Hawthorne [3] stated that the ectopic kidney is one which by reason of its abnormal embryologic development does not occupy the normal renal position. This anomaly is rare in comparison with the frequent condition of acquired renal ptosis, but the two conditions are easily differentiated.

Mackenzie and Hawthorne observed 11 cases of ectopic kidney in 15,000 admissions to their general service; in 6 instances the condition occurred among male patients and in 5 among female patients. Among the men, the ectopic kidneys of 4 were situated on the right side in the lower lumbar region or the upper sacral region. One was on the left side and was pelvic in type, and 1 showed a left crossed ectopy with lateral fusion to the right kidney. All of the 11 patients had symptoms

3. Mackenzie, D. W., and Hawthorne, A. B.: The Ectopic Kidney, Tr. Am. A. Genito-Urin. Surgeons **30**:121-139, 1937.

referable to the displaced kidney. In 5 cases there were pressure symptoms but infection was not present.

The authors concluded that congenital displacement of the kidney is rare, occurring once in every 1,000 cases, although some types of this anomaly are seen more frequently than others. Infection, hydronephrosis and formation of calculus frequently are associated with this abnormality. Symptoms were present in all of Mackenzie and Hawthorne's cases, although they were not always considered urologic symptoms at the onset. Pelvic ectopia among women frequently occurs during pregnancy, and in such cases it can be dealt with by cesarean section before term. Elevation of the kidney, although at times successful, is usually a failure owing to the shortness of both the ureter and the renal pedicle.

Lower [4] stated that there are two types of cases in which one may be called on to treat the single diseased kidney: (1) cases of congenital absence of one kidney or congenital solitary kidney and (2) cases of acquired single kidney in which nephrectomy has been performed. With the first condition, congenital single kidney, there is no way of anticipating the disease. With the second condition, acquired single kidney, the possibility of subsequent disease may be anticipated by noting at the time of operation the pathologic changes in the kidney that is removed. In a series of 325 cases of nephrectomy the condition most frequently necessitating removal of a kidney was calculous pyonephrosis. Of the patients with this condition, 9.8 per cent had stone in the other kidney at the time of nephrectomy.

Tuberculosis was the condition for which the next largest series of nephrectomies was performed. Of the patients with this type of involvement, 12.36 per cent later had trouble with the remaining kidney, although tuberculosis could not be demonstrated at the time of the operation. The next series comprised cases of hydronephrosis; 10 per cent of the patients had trouble in the remaining kidney.

From the investigation of this series of cases and from his own experience in dealing with the diseased single kidney, Lower concluded that the first step should be one of conservatism. Although there is a large reserve in the kidneys under normal conditions, there is no reason why too much of this reserve should be sacrificed unless it becomes an absolute necessity. He suggested that conservative treatment in some cases would be better than a radical operation, especially when the lesion is likely to be bilateral. When the physician is confronted with a solitary diseased kidney, naturally there is only one procedure, that

4. Lower, W. E.: The Problem of the Single Diseased Kidney. Tr. Am. A. Genito-Urin. Surgeons **30**:113-120. 1937.

is, conservation. When the symptoms are caused by obstruction the kidney must be drained either by ureteral catheterization or by pyelotomy or nephrostomy.

Calculus.—After a review of the material in one of the large clinics in Vienna, Bibus [5] came to the conclusion that mechanical factors are largely responsible for the formation of renal stones as well as vesical stones. Disturbance of mobility, that is, formation of residual urine in the upper part of the urinary tract, is the most important factor. He concluded that urinary infections also influence the formation of stones. When stones occur bilaterally, Bibus stated that the surgeon should choose for the first operation neither the kidney which is in better condition nor that which is more diseased, on the basis of these facts alone; the kidney which endangers the life of the patient or which is itself in danger of destruction should be treated first.

Randall, Eiman, and Leberman [6] stated that calcium plaques in the renal papilla were observed at necropsy in 140 of 609 cases, that is, in 22.9 per cent. In the same series of necropsies 49 renal papillae were observed with stone adherent thereto, and in practically every instance the stone was growing from a deposit of calcium in the papillary wall. In 25, or 4.1 per cent, of the 609 cases stone was observed at necropsy. They attempted but failed to reproduce this formation of calcium plaques in lower animals by administration of diets deficient in vitamins.

A staphylococcus toxoid was concentrated by the rabbit's kidney to from two and a half to sixty times its concentration in the blood plasma. The administration of a stable streptococcus hemolysin leukocidin effects highly suggestive results, causing local damage to the epithelium of the collecting tubules. After the administration of parathyroid extract to dogs for six months a calcium plaque was observed in one renal papilla, identical with that which had been seen in man. It was pointed out that the occurrence of renal calculus in man is essentially only a symptom of some underlying pathologic condition of a renal papilla and that its entire development is a slow, chronic process. Acute symptoms produced in the laboratory with experimental subjects are not comparable with the clinical picture.

Papayoannou [7] stated that he has had good results in the removal of giant coralliform stones by dividing his operation into two or even three stages. Stage 1 consists of exposure of the kidney and complete

5. Bibus, B.: Urolithiasis bilateralis, Ztschr. f. urol. Chir. u. Gynäk. **43**: 293-332 (Aug.) 1937.

6. Randall, A.; Eiman, J. E., and Leberman, P. R.: Studies on the Pathology of the Renal Papilla: Relationship to Renal Calculus, J. A. M. A. **109**:1698-1702 (Nov. 20) 1937.

7. Papayoannou, T.: La lithonéphrotomie en deux ou plusieurs temps, J. d'urol. **44**:242-249 (Sept.) 1937.

exteriorization of its convex external border, compresses being placed about it to keep open the surgical incision of the walls. Stage 2 consists of nephrotomy performed by thermocautery, to drain out the pus and remove the calculi if they are mobile. If, however, they are ramified and coralliform and are adherent to the renal parenchyma, their removal is postponed and is performed as a third stage, twenty-four or forty-eight hours later.

Lithonephrotomy in two or three stages is indicated principally in cases of unilateral or bilateral calculosis in which infection is severe, renal function deficient and medical treatment inefficacious. In such a case the patient becomes worse from day to day, possibly owing to pyonephrosis, uremia or glycosuria or to a poor cardiac condition. Unless an emergency arises the patient first should be put in the best possible condition; his resistance should be built up so that he can bear the operation satisfactorily, without suffering from shock. All the usual examinations and tests are carried out. Vaccination, especially autovaccination, prior to operation is an excellent measure to prevent septicemic complications. He should be fortified by injections of serum containing dextrose; the myocardium and the digestive system must be cared for meticulously as an indispensable part of the preparation. The least negligence in carrying out these details may cause disaster.

An illustrative case is reported in which the good results are attributed to performance of the operation in three stages, preceded by the building up of the patient's powers of resistance. The author stated that if he had used this technic in one of his early cases, to which he referred, operative shock and death of the patient would not have occurred. Experience in the treatment of 10 patients since that time, on all of whom he performed the operation in two or three stages, led him to report the details of his successful management.

One hundred and seventy-seven patients who had nephrolithiasis but who were not operated on at the time the diagnosis was established were observed by Priestley and Braasch[8] for an average of eleven years to determine their subsequent clinical course.

It was noted that: (1) Eighty-one and eight-tenths per cent of all unilateral stones and 97.8 per cent of all bilateral stones that were not removed surgically caused further symptoms referable to the urinary tract; (2) "silent" stones caused subsequent symptoms less frequently (66.66 per cent) than did stones which previously had caused pain (96.6 per cent); (3) large stones caused subsequent symptoms and necessitated later operation more frequently than did small stones; (4) stones in a calix caused subsequent trouble less often than did stones

8. Priestley, J. T., and Braasch, W. F.: Late Results in the Conservative Management of Nephrolithiasis, J. A. M. A. **109**:1703-1705 (Nov. 20) 1937.

in the pelvis; this was especially true of stones in the tip of a calix; (5) a kidney which contained a stone but which was normal on pyelographic examination caused serious symptoms less frequently than did a kidney which was definitely abnormal on pyelographic examination; (6) impairment of renal function increased the likelihood of serious symptoms and the necessity for subsequent operation, and (7) the presence of gross infection in association with stone definitely increased the incidence of subsequent symptoms referable to the kidney.

Tumor.—Patch [9] reported 3 cases of renal tumor. The first was carcinoma of a crossed heterolateral ectopic kidney without fusion.

The patient, a man aged 51, had the symptoms of slight enlargement of the prostate gland and slight transient hematuria for one year. He had noticed fulness in the lower part of the abdomen during this time. Examination gave evidence of moderate enlargement of the prostate gland; a mass was present in the right lower quadrant of the abdomen, extending upward to a point just below the level of the umbilicus. Retrograde pyelographic examination gave evidence of slight dilatation of the pelvis of the right kidney. The left catheter crossed the midline and extended upward to the level of the second sacral segment. The left kidney was not injected. The preoperative diagnosis was tumor in a crossed heterolateral ectopic kidney without fusion. This diagnosis was confirmed at operation. The tumor was a large clear-celled carcinoma of the hypernephroid type.

Patch discussed the nomenclature and the reported cases of crossed renal ectopic kidney, both fused and nonfused, and concluded that there has not been a previous report of a tumor associated with crossed heterolateral ectopia without fusion.

Borchardt described an adenoma weighing 12 pounds (5,443 Gm.), which occurred in what he considered a congenitally crossed ectopic kidney, but Patch [9] said that it undoubtedly was an acquired crossed variety, the ectopia being the result of displacement by the enormous tumor. Six other cases have been reported of acquired crossed ectopia from displacement by a large tumor or cyst.

In the second case a malignant leiomyoma occurred in a man, aged 55, who gave the clinical history and had the symptoms and signs of a right renal tumor. The mass was removed; it contained an infiltrating tumor almost entirely replacing the right kidney and invading the renal vein. Sections proved it to be leiomyoma which in some places had undergone sclerosis and in others showed sarcomatous change.

Small leiomyomas frequently are found at necropsy; such tumors, however, have little clinical significance. Patch's case makes the eighth

9. Patch, F. S.: Three Unusual Primary Kidney Tumours, Brit. J. Urol. **9**:339-358 (Dec.) 1937.

case of large renal tumor reported. Six of the tumors occurred in women and 2 in men. Four of the tumors were malignant.

The third unusual primary tumor of the kidney was a malignant transitional cell papilloma with local metastasis, arising in a loculus of an old hydronephrotic atrophic region in which there had been obstruction at the ureteropelvic junction owing to kinking, bands and adhesions. A malignant papilloma filled several of the loculi of the sac.

Hydronephrosis from obstruction of the renal pelvis by papillary tumors is frequent. No similar case of malignant papilloma arising in a loculus of an old hydronephrotic sac has been reported.

Bailey and Harrison [10] reported 5 cases of large benign renal neoplasm, discussing the pathologic picture and clinical behavior of the lesions. They stated that the problem of operative removal of large benign renal tumors is chiefly a question of correct approach. In 4 cases in this series, in which the tumor was removed by operation, the procedure was carried out by transperitoneal approach. In 1, removal was attempted through a lumbar incision but the renal pedicle was difficult to secure. The procedure was abandoned, therefore, and the tumor later was removed transperitoneally. The vascularity of the tumor, so strikingly demonstrated by the distended venous channels on its surface, is no longer a problem once the renal pedicle has been ligated.

Large dilated blood vessels on the surface of the tumor were present in all the cases. Bailey and Harrison emphasized this fact on account of the frequent presence of the same condition in association with malignant tumor of the kidney. Such a condition does not necessarily signify that the tumor has extended into the renal vein. It is reasonable to assume that the mere bulk of the new growth may so compress the renal vein as to cause dilatation of its collateral vessels. After the operation all 4 patients did well, and none of them had any recurrence of tumor.

The 4 patients were part (5.8 per cent) of a series of 68 patients on whom nephrectomy was performed for tumor. In view of the infrequency with which hypernephroma reaches such a size before operation is performed, the proportion of benign lesions among large renal neoplasms is even greater. Bailey and Harrison concluded, therefore, that patients who have large tumors and who give no evidence of metastasis always should be subjected to operative exploration.

Alcorn [11] reported a case in which a Wilms tumor occurred in an adult. He stated that Kilbane and Lester in 1929 found only 15 such

10. Bailey, O. T., and Harrison, J. H.: Large Benign Renal Neoplasms: Their Pathology and Clinical Behavior, with Report of Five Cases, J. Urol. **38**: 509-529 (Dec.) 1937.

11. Alcorn, K. A.: Wilms' Tumor in an Adult: Report of a Case, Proc. Staff Meet., Mayo Clin. **12**:692-694 (Nov. 3) 1937.

cases described in the literature. Since then several additional cases have been recorded.

The patient described by Alcorn [11] was a man aged 45, who noticed a swelling in the region of the left kidney for six weeks. During this time he noticed aching pain in this region and lost about 35 pounds (15.9 Kg.). Hematuria had not occurred. Physical examination revealed an emaciated man with a large fixed mass about the size of a grapefruit in the left renal region. An intravenous urogram showed no evidence of function on the left side. There was no clinical or roentgenographic evidence of metastasis. The right kidney appeared normal. Nephrectomy was performed on the left side, and the pathologist reported a Wilms tumor weighing 1,310 Gm., which had destroyed 90 per cent of the renal substance. The immediate postoperative convalescence was entirely satisfactory. A course of five roentgen treatments was given soon after the operation and was repeated one month later, at which time a general examination of the patient showed essentially normal conditions and a gain in weight. Three months later the patient was reexamined. At this time he was emaciated, and there was a large, firm mass in the lower half of the abdomen. There were many obvious regions of metastasis present. Inasmuch as a correct preoperative diagnosis of Wilms tumor was not established, a preliminary course of roentgen therapy was not given prior to operation.

Of 95 patients who had renal carcinoma and whose cases were reported by Fetter,[12] 58 (61 per cent) were subjected to operation, and 17 (29.82 per cent) of these were living after periods ranging from five months to thirteen years and three months; 36 (63.15 per cent) at the time of the follow-up had died, including 6 (5.2 per cent) who died after the operation.

Renal neoplasms are considered renal carcinoma because true columnar epithelial cells forming definite acini and papillae may be demonstrated. The term hypernephroma is used only to refer to tumors of adrenal tissue.

The surgical approach to the kidney should depend on conditions in the given case and on the surgeon's judgment. With the aid of preoperative irradiation many renal tumors decrease in size; the lumbar route, therefore, may be employed more frequently in the future than it has been in the past.

Fetter [12] concluded that preoperative irradiation is a definite aid to surgical intervention in the practical management of such neoplasms. He concluded also that routine postoperative irradiation has extended the period of survival of many patients.

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12. Fetter, T. R.: Renal Carcinoma: A Study of Ninety-Five Cases, with Follow-Up Notes on Thirty-Six, J. A. M. A. **110**:190-196 (Jan. 15) 1938.

Higgins [13] reported the cases of 5 patients who had squamous cell carcinoma of the renal pelvis, seen at the Cleveland Clinic. Including the records of their cases, the literature now contains 64 reports of squamous cell carcinoma of the renal pelvis.

The relation between leukoplakia and squamous cell carcinoma of the renal pelvis frequently is cited in the literature. The striking relation between renal calculi and squamous cell carcinoma has been noted by many observers. It has been stated by some authors that the development of such metaplastic changes may be induced by long-continued irritation due to chronic inflammation of renal calculi. This seems especially probable, because a review of a number of reports of cases indicates that the presence of chronic inflammation of the renal pelvis or calculi seems definitely to antedate the presence of the malignant lesion.

No symptoms are definitely pathognomonic of squamous cell carcinoma of the renal pelvis. Each of Higgins' patients complained of symptoms referable to pyuria due either to a calculus or to chronic inflammation. They also complained of pain in the back. The latter symptom has been present in 43 per cent of cases in the collected series. Loss of weight is a late manifestation, usually occurring after metastasis has taken place.

Two types of lesions predominate: In the first type the cells early invade the renal parenchyma and eventually replace it. The second type of lesion is confined chiefly to the renal pelvis; the region is covered with tumor which in some areas has a papillary appearance. With this type, involvement of the ureteropelvic junction occurs earlier, and a severe degree of hydronephrosis, with atrophy of the renal parenchyma, is found.

Early diagnosis followed by nephrectomy is the procedure of choice. In Higgins' series, in which high voltage roentgen therapy was employed preoperatively, there was no evidence of reduction in the size of the tumor. Postoperative roentgen therapy is advisable.

The prognosis is grave because of the frequency of metastasis. In a review of the literature, Higgins was unable to find the report of a patient who was free from metastasis at the end of five years.

Patch [14] reported 9 cases of tumor of the pelvis and ureter. Six of the tumors were in the pelvis, 2 being benign papilloma, 1 malignant papilloma, 2 squamous cell carcinoma (in 1 case associated with leukoplakia) and 1 transitional cell carcinoma.

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13. Higgins, C. C.: Squamous Cell Carcinoma of the Kidney Pelvis, Tr. Am. A. Genito-Urin. Surgeons **30**:13-33, 1937.

14. Patch, F. S., in discussion on Caulk, J. R.: Tumors of the Renal Pelvis and Ureter, Tr. Am. A. Genito-Urin. Surgeons **30**:71-73, 1937.

Patch recalled the tendency of papilloma of the pelvis to recur farther down in the urinary tract. In addition to complete ureterectomy performed at the time of nephrectomy, careful observation of the bladder during a long postoperative period is advisable.

Patch pointed out also that the picture in cases of pelvic and ureteral tumor, particularly of the latter, is likely to be dominated by hydronephrosis; careful urographic examination is particularly important in such cases.

Wolff and Donat [15] cited the report of Lindau, who in 1926 described the anatomic picture of a dysontogenetic disease which he called "angiomatosis of the central nervous system." The principal changes are the formation of hemangioma in different parts of the brain, the medulla, the spinal cord and the retina, associated with malformations in other organs, that is the liver, the pancreas and the kidneys. The complex malformations of the kidney have never been described. Wolff and Donat examined a man aged 37 who had Lindau's disease; cystic hypernephroid changes had occurred in both kidneys. They gave a detailed description of the anatomic changes in this case, with photographs. There remained in both kidneys very little normal parenchyma. The portion destroyed was replaced by tumor containing a mixture of cysts and hypernephroma. Twelve such cases have been described in the literature.

Ordinary cysts of the kidneys are frequently associated with hemangioma of the central nervous system. Adenoma and fibroma are rarer.

In two thirds of all cases of Lindau's disease there is evidence of malformation of the kidneys, possibly originating in the development of the organ. The coincidence of malformation of the kidneys and lesions of the central nervous system characterizes two other diseases: tuberous sclerosis of the brain and the dysencephalia splanchnocystica of Leiden.

Hydronephrosis.—Walters, Cabot and Priestley [16] stated that plastic operations on the renal pelvis are indicated (1) if hydronephrosis producing symptoms is present on both sides; (2) if hydronephrosis is present in a solitary kidney, and (3) if there is hydronephrosis of one kidney in the presence of a damaged or abnormal kidney on the other side.

Since 1929 various types of plastic operation have been carried out in 71 cases at the Mayo Clinic up to January 1937. In this group there was a mortality during hospitalization of 2.81 per cent.

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15. Wolff, K., and Donat, R.: Die Nierenveränderungen bei der Lindauschen Krankheit an Hand einer Beobachtung von cystisch-hypernephroider Umwandlung beider Nieren, Ztschr. f. urol. Chir. u. Gynäk. **43**:272-292 (Aug. 12) 1937.

16. Walters, W.; Cabot, H., and Priestley, J. T.: Operative Results in Noncalculus Hydronephrosis: Results in Seventy-One Plastic Operations, J. Urol. **38**:688-693 (Dec.) 1937.

Conclusions were based on a study of 46 of the 71 cases, 25 being excluded for the following reasons: In 8 cases there was not satisfactory evidence in regard to the conditions at reasonable periods after the operation; 2 patients died, and in 15 cases nephrectomy was done.

The types of operation were as follows: (1) resection of the renal pelvis (21 cases); (2) resection with reimplantation of the ureter (9 cases); (3) reimplantation of the ureter (3 cases); (4) division of one or more abnormal vessels to the lower pole (2 cases); (5) ureterolysis (2 cases); (6) ureteropyeloneostomy (4 cases); (7) miscellaneous procedures (5 cases), and (8) nephropexy combined with various of the procedures mentioned (19 cases).

Nephrostomy alone was employed in 5 cases. Nephrostomy as an adjunct to various plastic operations was employed in 48 cases.

Secondary nephrectomy was required in 15 cases, or 21.12 per cent. It does not appear that these unfavorable results were associated with any particular type of operation. Thus, in 9 of the cases resection was performed, whereas in each of the remaining 6 cases a different type of operation was done. It will be noted that 12 of the 15 patients were treated by nephrectomy within the first year; 1 two and a half years later, and 2, seven years later.

With the exclusion of certain cases for various reasons, Walters, Cabot and Priestley[10] had 46 cases on which to base their report on operative results in cases of hydronephrosis; reports were made on the basis of pyelographic evidence (26 cases) and also on the basis of reports by letter (20 cases). They have not considered as conclusive any pyelographic evidence which was obtained less than seven months after operation. The group of cases in which reported results were based on pyelographic evidence includes, therefore, cases in which pyelographic studies were done from seven months to more than seven years after the operation.

Considering first all of the various types of operations together, they have classified on pyelographic evidence the results in 5 cases as excellent and in 8 as good; in 5 others the condition of the patients was classified as improved, and in 8 others as not improved. Of the remaining cases, classified on the evidence of letters, in 7 the results have been classified as good; in 8 others the condition of the patients was classified as improved, and in 5 others as not improved. The total results, from evidence both of the pyelogram and of the letters, are as follows: in 5 cases, excellent; in 15, good; in 13, condition improved; and in 13, condition not improved. In a word, 33 of the 46 patients (71.7 per cent) have benefited definitely by the operation, and 13 have not.

Judged by the aforementioned criteria, the results for patients for whom the operation was classified as "resection of the renal pelvis" (21 patients) indicate that of 9 for whom the reported results were based

on pyelographic evidence, the condition of 4 was classified as excellent; that of 1, as good; that of 1, as improved; and that of 3, as not improved. Classified as to results reported on the basis of letters, among 12 patients, the condition of 4 was classified as good; that of 5, as improved, and that of 3, as not improved.

In the cases in which the operation was classified as "resection of the renal pelvis with reimplantation of the ureter" (9 cases), the results based on pyelographic evidence indicate that the condition of 3 patients was classified as good and that of 1 as improved; in cases in which results were reported on the basis of letters, the condition of 2 patients was classified as good; that of 1, as improved; and that of 2 as not improved.

With the help of Rein's thermostromuhr Maatz and Krüger [17] examined the different reactions of the blood stream of the kidney in experimental hydronephrosis in dogs. A rise in the blood pressure of the renal pelvis calls for a decline in the blood supply of the kidney. This decline is the same in the arteries and in the veins. It is proportional to the height of the pressure in the renal pelvis, but is much lower than was anticipated from the results of earlier anatomic investigations. The explanation of this is an active dilation of the blood vessels. The intraparenchymal rise in fluid content which is observed in the renal tissue as early as two hours after ligature of the ureter does not cause a diminution in the flow of the blood stream. The blood supply of a fully developed hydronephrotic kidney is less than 25 per cent inferior to the blood supply of the opposite healthy kidney with its compensatory hypertrophy. In cases of closed hydronephrosis of three weeks' duration even the most vigorous stimulation of diuresis causes only a slight rise of pressure in the renal pelvis; hence a serious mechanical disturbance of circulation of the blood in this state is improbable. The inhibition of the renal blood supply does not seem to be of such importance as a cause of atrophy of renal parenchyma in cases of hydronephrosis as is accepted at present.

Lubash and Madrid [18] attempted a modification of the orginal Küster operation, ureteropyeloneostomy for hydronephrosis. The ureter is removed from its original site as near its insertion in the pelvis as possible, as the strictured region is utilized in its reimplantation. From this point on, the method as originally given by Küster is carried out for the most part. There is a difference, however, in the method of anastomosis. The ureter is incised downward on its anterior and pos-

17. Maatz, R., and Krüger, E.: Das Verhalten der Nierendurchblutung in der experimentellen Hydronephrose, Ztschr. f. Urol. **31**:756-770 (Nov.) 1937.

18. Lubash, S., and Madrid, A.: Uretero-Pyeloneostomy for Hydronephrosis, with Case and Experimental Reports, J. Urol. **38**:634-642 (Dec.) 1937.

terior surfaces for a distance of 2 or 2.5 cm., and after its insertion into its new mouth at the most dependent portion of the renal pelvis the straps of the ureter are drawn outward laterally from the pelvis through two small stab wounds on either side of the new neostomy, and a mattress suture is employed to fix them in position. The knots are placed outside the renal pelvis. From this point on, Papin's method of transrenal drainage and resection of the redundant pelvis is carried out. Both the Garoeau catheter that serves as a splint for the new anastomosis and the Pezzer catheter that drains the kidney are brought out through the same nephrostomy wound. Nephropexy is employed if the kidney has been mobilized.

Work on 4 experimental subjects with this method has proved gratifying. The experimental stage has been divided into two separate periods, the work during first period being limited to the ligation of the ureter and the formation of hydronephrosis. The ligature about the ureter was tied 2.5 cm. from its renal insertion, by means of silk threads.

A period of two to five months was allowed to elapse before the second stage (plastic repair) was performed. All experimental subjects survived. The tests for renal function, as performed by the insertion of the Pezzer catheter, showed return of function in a very short time after plastic repair.

Hepler [19] stated that from the etiologic standpoint dilatation of the upper part of the urinary tract, occurring in children, may be divided into three types: (1) that due to mechanical obstruction, most frequently to congenital fibrosis, muscular hypertrophy or exaggerated constriction at the points of normal anatomic narrowing, that is, the ureteropelvic and ureterovesical junctions and the vesical outlet; (2) that occurring as a sequela of a neural condition, either central or peripheral, involving the bladder (such as poliomyelitis, cerebrospinal syphilis, spina bifida, toxic neuritis or the less definite dysfunctions classified as idiopathic); and (3) that for which no obvious cause, either mechanical or dynamic, can be demonstrated.

Hepler [19] discussed functional imbalances at the ureterovesical junction as a possible cause in some cases of dilatation of the third type.

The lower and intramural part of the ureter and the vesical trigon may be considered an anatomic and physiologic unit. These structures have a common embryologic origin which is distinct from that of the rest of the bladder. The muscles of the trigon are formed from a continuation of the longitudinal fibers of the ureters, the lateral extensions forming Bell's muscle and the mesial extensions, which unite with

19. Hepler, A. B.: Nonobstructive Dilatations of Upper Urinary Tract in Children, J. A. M. A. **109**:1602-1606 (Nov. 13) 1937.

those of the opposite side, forming Mercier's bar. Fibers from the central muscle of the trigon loop about the intramural portion of the ureter.

Pharmacologically it has been shown that this unit has a common nerve supply and responds to drugs differently from the rest of the bladder. It receives fibers from the hypogastric nerves only and stimulation of these nerves produces strong contraction of the intravesical portion of the ureter, where the ganglions are most numerous, and of the adjacent trigon.

This neuromuscular arrangement has considerable functional significance; although there is no circular muscle comparable to the anal sphincter, it acts in a similar manner and takes a part in ureteral dynamics. There is active relaxation with opening of the orifice synchronous with the termination of the peristaltic wave. This is followed by a period of contraction, or expulsive effort, at which time the orifice is of pinpoint size and is drawn upward and outward with the adjacent trigon or ureteral mound. There may then be partial relaxation followed by a second contraction, or expulsive effort, after which there is complete relaxation and the slitlike orifice returns to its normal position and shape. The process is comparable to the action of the levator ani muscles in completing the act of defecation.

There may be disturbances in ureteral activity which are comparable to those recognized in like mechanisms for the emptying of a tube of involuntary or smooth muscle with a sphincter at its distal end, such as the gastrointestinal tract. Two types of functional imbalance at the ureterovesical junction are recognized: (1) increased tonicity, or spasm, and (2) absence of the usual active relaxation synchronous with the termination of ureteral peristalsis, or achalasia. The resistance to ureteral emptying caused by these dysfunctions sets in motion the same physical and dynamic factors which produce dilatation in cases of mechanical obstruction. Compensation is more likely to occur in cases of functional imbalance than in cases of mechanical obstruction, because resistance to ureteral emptying is likely to be less unyielding; hence the observation of ureterectasis out of proportion to pelvic dilatation and the absence of elongation and tortuosity.

In some cases congenital idiopathic dilatation considered as a primary embryologic developmental defect may in fact be secondary to a segmental imbalance or to abnormal activity of the sphincter. Hepler [19] discussed 4 cases in which nonobstructive dilatation was observed among children; the condition was assumed to be caused by achalasia at the ureterovesical junction. Hepler also gave criteria for the recognition of this condition.

The association of megaloureter and megalocolon in the case of a child was of interest in view of the contention that the pathogenic

mechanisms of the two conditions are similar. The indications for treatment of a condition which is so little understood and concerning which there have been so few clinical data are not clearly defined. The following methods have been advocated: (1) presacral neurectomy; (2) plastic resection of the ureterovesical junction; (3) incision of the junction by high frequency current, and (4) gradual dilation for high degrees of obstruction.

Foley [20] described a new plastic operation for stricture at the ureteropelvic junction. A large incision which provides adequate exposure and complete freeing of the kidney is essential. By careful examination the exact anatomic relations responsible for obstruction are determined. Adhesions between the pelvis and the ureter are severed completely, which accurately exposes the ureteropelvic junction. The latter is examined carefully by inspection, by palpation and, if necessary, by instrumental exploration through a small pyelotomy. By these means the presence or absence of "stricture" is determined and the question of the need for plastic operation is answered.

The kidney and ureter are held in position to give facility in accurately placing the Y incision in the pelvis and ureter. The stem of the Y is placed in the lateral wall of the ureter and thus will face the pelvis when normal position is restored. The incision is carried through the ureteropelvic junction and downward in the medial wall of the pelvis for an appropriate distance below the ureteropelvic junction. From this point the incision continues as two diverging limbs in the lower medial wall of the pelvis, in the form of an inverted V. The incision in the ureter should equal in length the incision in the pelvis plus the length of the V-shaped flap. The triangular opening in the pelvis and the triangular flap of pelvic wall when turned down face directly the incision in the ureter.

The apex of the flap approximates directly the lower angle of the ureteral incision. By closely spaced interrupted sutures of 0000 chromic catgut embracing only the muscularis (with careful avoidance of the mucosa) the edges of the ureteral incision and the edges of the triangular defect in the pelvis are approximated directly, the tip of the flap fitting neatly into the lower end of the ureteral incision.

When the suturing is completed a soft rubber catheter of size 10 or 12 French is introduced through a small stab opening on the posterior surface of the pelvis and is directed into the ureter for a distance of 6 or 8 cm. A number of small fenestrations are cut in the portion of catheter that is to lie within the pelvis. The catheter serves as a splint for the sutured segment and provides for drainage of urine from the

20. Foley, F. E. B.: A New Plastic Operation for Stricture at the Ureteropelvic Junction: Report of Twenty Operations, J. Urol. **38**:643-672 (Dec.) 1937.

pelvis. It is left in place for about a week. A second catheter, extending only into the pelvis, is introduced for use in through and through irrigation.

The operation described has been employed 20 times, in 19 different cases; this is one of the largest series of plastic operations for hydronephrosis to be reported.

In practically all cases reexamination by pyeloureterographic study, functional tests and reports as to relief of symptoms were obtained at long intervals after the operation. In almost half the cases the time from the date of operation to the preparation of the report was seven years or more and 15 of the 19 patients were living at the time of the report. Symptomatic relief was obtained in all cases, and in all but 3 cases the report was obtained a year or more after the operation. In 6 cases it was obtained seven years or more after the operation. In all but 1 case (in which death occurred postoperatively) functional tests and reexaminations according to the methods mentioned were made to determine the condition after operation.

Quinby [21] stated that the treatment of hydronephrosis depends for its success first and most appreciably on the absence of infection both at the time of operation and after operation. This factor is of such importance that every effort should be made to sterilize the kidney by the administration of urinary antiseptics both by mouth and by local application before any plastic procedure is undertaken. Preliminary nephrostomy with antiseptic lavage throughout the drainage tube may be a wise first step for obstinate hydronephrosis accompanied by infection. It has been Quinby's experience that the promotion of better drainage of the kidney by a plastic operation will not in itself be sufficient to allay the infection. Even if the plastic operation is followed by adequate healing the infection will persist, and it will eventually destroy the kidney.

There are two main types of hydronephrosis: (1) that due to anomalous development of the kidney and its appendages and (2) that secondary to the formation of stones or to obstruction in the urinary tract. Hydronephrosis of the first type due to arterial anomaly or, more rarely, to venous anomaly is treated with outstanding success by some form of plastic correction of the underlying anomaly. Other, more gross anatomic anomalies offer still further problems, for example, renal fusion or ectopia. Cases of hydronephrosis of the second type offer, on the whole, much less hopeful prospect of cure by a plastic operation, for the lesion often is bilateral and when first seen is accompanied in many instances by severe infection. In this group, correction of the hydronephrosis itself frequently is of secondary importance to relief of the

21. Quinby, W. C.: Factors Influencing the Operative Procedure in Hydronephrosis, J. Urol. **38**:673-679 (Dec.) 1937.

underlying pathologic condition. If this can be accomplished, the hydronephrotic kidney will be found in many instances to retain a respectable amount of function and will cause no symptoms, although its pelvis may seem grossly abnormal on pyelographic examination. Unconquerable infection, however, will spoil all surgical efforts. Nephrectomy, when possible, is then the only relief.

Kafka [22] reported the case of a girl aged 4 months who had congenital hydronephrosis on the left side. The condition was so advanced that the kidney was a unilocular cyst with a thin wall of renal parenchyma. Hydronephrosis resulted from atresia of the ureter, which began at the pelvis and extended downward, making a diverticular pouch about 1 cm. in length. Nephrectomy was performed, and the child recovered. At the same time there was congenital dislocation of the right hip, for which operation was performed a year later. Six years later the child was in excellent condition.

Crabtree [23] stated that pregnancy does not alter the position of the kidneys. If the renal shadow gives evidence of an abnormal relation to other organs, the condition is generally due to anomalies antedating pregnancy. Abnormalities of the calices, pelvis and the ureter may be attributable to pregnancy, but rounded calices have not the same significance when they occur in pregnant women as when they occur in patients who are not pregnant. Congenital abnormalities of the pelvis and ureter and preexisting alterations caused by disease generally are recognizable in cases of pelvic dilatation due to pregnancy, as pregnancy may exaggerate previously existing conditions.

When intravenous pyelographic examination shows the lower two thirds of the ureter completely filled, the condition should be considered pathologic. There is sufficient evidence to reestablish the fact that relaxation of the muscles of the renal tree associated with pregnancy may be due to the effects of pregnancy on the endocrine glands.

The excretion of drugs used for intravenous pyelographic examination is apparently retarded by pregnancy both of women and of experimental animals. Decreased motility in cases of large pelvic and ureteral dilatations interferes with diffusion of the excreted dye and thus produces a less satisfactory demonstration of the pelvis and ureter.

The essential differences between a chronic obstructive lesion and an obstructive lesion which has its origin in pregnancy must be recognized. The former is characterized by hypertrophy of the muscles, decompensation after the limit of hypertrophy has been reached and changes due to fixation, which limit indefinite dilatation.

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22. Kafka, V., Jr.: Ein Fall von Hydronephrose bei einem 4 Monate alten Säugling bei gleichzeitigem Bestehen einer Hüftgelenksluxation, Ztschr. f. Urol. **31**:602-606 (Sept.) 1937.

23. Crabtree, E. G.: Hydronephrosis of Pregnancy, J. Urol. **38**:605-619 (Dec.) 1937.

The abnormalities in the pelvis and ureter which are attributable to pregnancy are distinguished by the absence of hypertrophy, probably a result of endocrine influence. Surgical treatment in the latter cases has a more favorable prognosis.

A number of occurrences of hydronephrosis cannot be explained by intrinsic obstructions, and it becomes necessary to search carefully for extrinsic causes. It must not be forgotten that extrinsic and intrinsic causes may coexist. Long-continued pressure on the ureter from the outside often produces damage within the ureter, resulting in inflammatory changes, fibrosis and obstruction, which may remain after the extrinsic cause is removed, thereby seriously impairing the symptomatic and pyelographic result. Bobbitt [24] divided these extrinsic causes into four groups: (1) aberrant polar vessels and fibrous bands, (2) renal, abdominal or retroperitoneal tumor, (3) trauma with defective innervation and (4) fibrosis of the ureter, due to irradiation or to involvement of the ureter by a malignant growth.

Ekehorn was probably the first to direct attention to the part played by aberrant polar vessels in the causation of hydronephrosis. By reason of the fact that aberrant vessels frequently lie close to the ureter there has been considerable opposition to his work. Bobbitt concluded that increased mobility of the kidney or inflammatory changes in the region of the ureteropelvic junction, or both, usually is the inciting factor in this type of obstruction. He has found fibrous bands or adhesions in a rather small percentage of cases.

Large abdominal tumors certainly must be listed as occasional causes of hydronephrosis, although in Bobbitt's experience they are seen rarely, owing probably to the fact that in these days of modern surgical treatment for such tumors operation is performed early and often the condition is so apparent that no pyelographic study is made.

Traumatic injuries to the kidney and the surrounding structures can cause hydronephrosis in different ways. Neuromuscular conditions also play an important role in hydronephrosis. Braasch explained that there is a group of cases in which pyelectasis occurs with no apparent cause for ureteral obstruction. He has noted a hypertonic condition of the muscles which produces contractions at the ureteropelvic junction so violent as to cause protrusion into the lumen, producing a true ball valve action.

In reviewing the intrinsic causes of hydronephrosis, Mathé [25] divided them into three categories: (1) congenital, (2) acquired and (3) traumatic.

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24. Bobbitt, R. M.: Extrinsic Causes of Hydronephrosis, J. Urol. **38**:562-573 (Dec.) 1937.

25. Mathé, C. P.: Intrinsic Causes of Hydronephrosis, J. Urol. **38**:574-592 (Dec.) 1937.

Congenital hydronephrosis unassociated with other anomalies of the urinary apparatus exists as a distinct clinical entity and is probably far more frequent than is conceded in the literature. Associated stones are caused by pre-existing stasis; accessory vessels and ptosis play a minor role and are factors only in the late stages of the development of hydronephrosis. Valve formation or high insertion of the ureter is a result of pelvic dilatation rather than its cause. Hydronephrosis frequently accompanies a malformation of the kidney or ureter, such as bifid and double pelvis and ureter, fused, ectopic and horseshoe kidney, aberrant distribution of blood vessels or congenital structure and valve formation of the ureteropelvic junction. With such conditions hydronephrosis may accompany the renal anomaly at birth; or poor drainage resulting from malformation may produce hydronephrosis later in life, superimposed infection playing an important role.

Acquired hydronephrosis resulting from mechanical obstruction at the ureteropelvic junction or the upper part of the ureter long has been recognized. In a great number of cases of hydronephrosis the condition is so caused. Of interest is the dynamic type of hydronephrosis due to neuromuscular dysfunction either associated or not associated with pyelonephritis.

Traumatic hydronephrosis is a clinical entity. It is usually the result of late sequelae of, and is occasionally the immediate result of, direct or indirect trauma to the kidney. Obstruction is produced by strangulation of the ureter due to cicatricial changes resulting from organization following extravasation of blood and urine in the perinephrium. In rare instances hydronephrosis is due to obstruction from blood clots, sudden displacement of the kidney or dislodgment of preexisting renal calculi.

Tuberculosis.—Mathé [26] has observed 6 cases of unilateral renal tuberculosis in which the condition occurred in children and adolescents aged 2, 10, 13, 16, 17 and 18 years, respectively. Four patients are living and in good health ten, eight, three and two years after operation, respectively. Two died six months and five years, respectively, after operation as the result of generalized spread of the disease.

In reviewing 4,698 cases of unilateral renal tuberculosis, Mathé found that this disease was present in 565 patients (12 per cent) between the ages of 1 and 20 years; there were 20 occurrences (0.42 per cent) in children from 1 to 5 years of age; 51 occurrences (1.08 per cent) in children from 5 to 10 years of age, and 494 occurrences (10.5 per cent) in adolescents between 10 and 20 years of age. The statistics

26. Mathé, C. P.: La tuberculose rénals de l'enfant, Arch. d. mal. d. reins **10**:517-544 (Nov.) 1936.

of autopsies show that the disease is much more frequent at the latter age (25 to 30 per cent more frequent).

Despite the perfection of cystoscopes of small caliber and despite the increased use of roentgenographic tests for renal function, many pediatricians and physicians do not always take advantage of these methods of research when they examine children suffering from chronic infection of the urinary tract.

Although autonephrectomy and quiescence of symptoms have been regarded as indications of spontaneous cure of renal tuberculosis, the treatment best suited to the unilateral type among children as well as among adults is nephrectomy, and if this operation is carried out sufficiently early it results in a large proportion of cures. It is probable that in cases of renal tuberculosis of the unilateral surgical type, in which the condition later may become bilateral, cure of the disease in the kidney is not effected. According to the reports, tuberculous kidneys that have undergone calcification, with total occlusion of the ureter and with cessation of symptoms, amount to about 0.5 per cent. Spontaneous cure probably never occurs. For this reason early nephrectomy is the procedure of choice and is the only means of relief for the children who compose the other 99.5 per cent of patients.

Pyelonephritis.—Wharton, Gray, and Guild [27] stated that only 2 of 30 girls and young women who had pyelitis in infancy and childhood and who were examined (on the average) nine and six-tenths years after the last attack of pyelitis were found to be in poor health. Only 1 had been treated for any urologic disease since the occurrence of pyelitis in childhood. This young woman had been an invalid owing to chronic urinary infection. She had lost one kidney, and the remaining kidney was hydronephrotic and infected.

Twenty-eight had had average good health since childhood; most were in excellent health. The vast majority had no complaints; symptoms, when present, could be elicited only by questioning. Follow-up urologic examinations showed that 17 (57 per cent) had definite abnormalities in the urinary tract at the time of reexamination. Of 9 who had had only one attack of urinary infection in childhood, 6 showed urinary abnormalities. Of 21 who had had recurring infections in childhood, 11 had urinary abnormalities at the time of reexamination.

General results of the reexamination showed that 10 had mechanical abnormalities demonstrable by intravenous urographic study. Ten had varying numbers of leukocytes in the catheterized urine. In 15 cases cultures of the urine yielded bacteria. Two patients had small stones.

27. Wharton, L. R.; Gray, L. A., and Guild, H. G.: The Late Effects of Acute Pyelitis in Girls, J. A. M. A. **109**:1597-1602 (Nov. 13) 1937.

One girl, aged 15 years, had a functionless kidney with practically no symptoms. Three young women had borne children; 1 had pyelitis while pregnant.

In a series of 200 cases of chronic pyelonephritis recently observed at the Mayo Clinic by Braasch,[28] bacilli of the colon group were found in 110 cases. Escherichia coli was present in 84 cases, or 42 per cent, and Aerobacter aerogenes in 26 cases, or 13 per cent.

Next in frequency, cocci are found in the urine in cases of chronic pyelonephritis. In the series of 200 cases they were found in 28, or 14 per cent. Their presence is noted often on microscopic examination of the urinary sediment when cultures are sterile. Some bacteriologists regard them not as etiologic factors but as unimportant secondary invaders and as being frequently the result of contamination.

Streptoccocci are found only occasionally in the voided urine in cases of chronic pyelonephritis and less frequently when the urine is catheterized. In the series of 200 cases of pyelonephritis they were present in only 8 cases, or 4 per cent.

Proteus was found to be the infecting organism in only 6 cases, or 3 per cent. This organism is not satisfied with being an indolent invader causing chronic infection; either it exercises its destructive activities so as to destroy the kidney with diffuse purulent infection or malignant formation of stones, or it disappears after a short period of infection.

In the series, bacterial pyuria was found in 44 instances, or 22 per cent. It was observed most frequently in cases of advanced renal infection of long standing accompanied by cicatricial changes or by impaired renal function.

A review of the 200 cases showed that the p_H of the urine, with but few exceptions, fell in the neutral zone, between 5.9 and 6.5.

A complication which frequently is observed in association with chronic renal infection is that of secondary formation of stone. In a series of 526 cases of chronic bilateral pyelonephritis observed at the clinic in the past seven years, secondary lithiasis was found in 28. Lithiasis secondary to chronic pyelonephritis is often bilateral, as is shown by the fact that stones were found in both kidneys in 9 cases of this group of 28, or 32 per cent. When bilateral the stones usually are multiple. Unilateral stones were found in 19 cases; they were single in all but 4. When there is chronic bilateral pyelonephritis and a stone is present in one kidney the renal infection usually is primary, because infection which occurs secondary to stone seldom is transmitted to the other kidney.

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28. Braasch, W. F.: Clinical Data Concerning Chronic Pyelonephritis, J. Urol. **39**:1-25 (Jan.) 1938.

Renal hematuria is not an infrequent complication; it occurred in 67 of 526 cases. It can be distinguished from other forms of renal hematuria because it is usually accompanied by evidence of infection, as a rule involving both kidneys.

In considering the treatment of chronic pyelonephritis, it is interesting to compare the remedies of yesterday with those employed today. Lavage of the renal pelvis and the bladder, formerly employed as a matter of routine, has been largely superseded by other therapeutic measures. Although eradication of infection is not to be expected by means of lavage, this measure is still indicated in cases of excessive pyuria and in the treatment of secondary hematuria.

Vaccines, which formerly were employed in spite of unconvincing results, are now largely discredited.

Reference frequently has been made to the possibility that foci of infection, such as occur about the teeth and also in the tonsils, the prostate gland and the uterine cervix, are sources of renal infection. Although such foci are often of clinical importance in the causation of acute or recurrent renal infection, they are not so important in the causation of chronic pyelonephritis. Removal of these foci does not usually have much effect on the course of chronic renal infection; the time for their removal is long past, because the infection has become so thoroughly intrenched in the renal tissues that removal of the original source no longer has much therapeutic value.

The presence of infection in the prostate gland and the seminal vesicles may be the cause of persisting renal infection; such infection apparently may act not as a distant focus but as a direct source of ascending infection. Efforts to eradicate renal infection are often futile because of subsequent reinfection from these persistent foci. Buchtel has shown that sulfanilamide is present in the prostatic secretion in sufficient concentration to be bacteriostatic. He stated that it is of material aid to massage in reducing prostatic infection. Although removal of infected teeth and tonsils has not directly benefited patients with chronic renal infection in many cases, experience has shown that it can materially affect the progress of infection of the prostate gland, and eradiction of these foci should be insisted on.

Deformity (demonstrable by urogram) which accompanies chronic pyelonephritis and which is regarded as characteristic consists of caliectasis and ureterectasis with cicatricial narrowing of the infundibula and the renal pelvis. The dilatation of both the ureter and the calices usually is adynamic. On the other hand, pyelectasis, which is comparatively infrequent, is likely to be the result of obstruction. Dilatation of the ureter is usually of greater diagnostic importance than is dilata-

tion of the calices. Adynamic or atonic ureterectasis may be explained by periureteritis affecting the trophic nerves which supply the ureteral wall.

Surgical treatment, the need for which is surprisingly infrequent in these cases, usually is not indicated unless one of the following conditions is present: some form of obstruction; localized, persistent infection; destruction of renal function; or atrophy. Such treatment was found necessary in only 3 per cent of the 526 cases of chronic pyelonephritis observed by Braasch [28] at the Mayo Clinic in the past seven years.

In the recent developments of chemotherapy, compounds have been produced which have given startling results: sulfanilamide and mandelic acid. Although sulfanilamide gives promise of being a potent factor in eradicating renal infection in many cases, in common with other similar drugs it is of greater value against acute than against chronic infection. There is a vast difference in the results obtained in treatment of chronic and of recent renal infection. Although most renal infections when acute, subacute or recurrent can be controlled by recently developed chemotherapy, the secondary and anatomic changes associated with chronic infection often will defy all treatment.

Eradication of chronic pyelonephritis is possible by prophylaxis and by thorough, intelligent treatment of acute and subacute infection. Treatment of urinary infection still demands the intelligent supervision of the urologist.

In 2 cases in which the patients were men reported by Albright, Dienes and Sulkowitch,[29] roentgenograms of the kidneys showed multiple deposits of calcium in the pyramids. The deposits were larger and of less uniform size than those seen in cases of nephrocalcinosis associated with hyperparathyroidism. Small gram-negative bacilli were present in the urine of both patients; the organism was identified as Haemophilus influenzae. The urine of both patients was constantly alkaline, probably owing to the property of H. influenzae to split ammonia from urea, and the deposits of calcium were presumably attributable to the alkalinity so produced. Sulfanilamide promptly eliminated H. influenzae from the urine, with resulting acidity of the urine.

Parenchymal Infection.—Hamer [30] stated that metastatic renal infection includes a group of lesions of the kidney, due to blood-borne infection, with which there is no urogenital abnormality acting as an accessory cause. The source of the infection is usually some remote peripheral focus, such as a carbuncle, a boil, an infected wound or an

29. Albright, F.; Dienes, L., and Sulkowitch, H. W.: Pyelonephritis with Nephrocalcinosis Caused by Haemophilus Influenzae and Alleviated by Sulfanilamide: Report of Two Cases, J. A. M. A. **110**:357-360 (Jan. 29) 1938.

30. Hamer, H. G.: Diagnosis and Treatment of Metastatic Renal Infection, J. Urol. **38**:530-540 (Dec.) 1937.

infection of the respiratory tract. The organism is usually a pyogenic coccus. The lesion is a miliary abscess, massive abscess, carbuncle, perinephritis or perinephric abscess. The clinical picture includes pain in the region of the affected kidney, costovertebral tenderness and fever of the septic type. The laboratory findings indicate that the urine is essentially normal; staphylococci may be produced in smears or cultures, and a large number of leukocytes may be present in the blood. Roentgenologic examination may give evidence of clouding of the renal region, obscuration of the shadow of the psoas muscle and scoliosis. Pyelograms may show compression, filling defects and inflammatory fixation of the kidney. Incision and drainage will effect a cure in the majority of cases. In a few the condition requires nephrectomy.

Embolism.—Westerborn [31] reported the case of a man aged 49 who had recurrent emboli from chronic endocarditis. The first embolus went to the brain, causing temporary paralysis of the left side of the body. Six months later an embolus lodged in the right femoral artery. This was removed, and the patient recovered. In the next four months he had two more emboli, to the mesenteric arteries and to the brain. He recovered completely. Two weeks later an embolus blocked the right renal artery. During attempted removal the thrombus slipped from the artery to the kidney and was crushed by hand as well as possible. After this maneuver the circulation in the kidney and the renal function were reestablished temporarily. Five weeks later this kidney was functionless, and nephrectomy was done. The kidney was atrophied to one-third its size at the first operation. Eight months later an embolus lodged in the left renal artery, with complete block. Eighteen hours later embolectomy was performed, but the circulation was never reestablished, and the patient died of uremia. This was probably the first time that operative removal of an embolus from the renal artery was attempted.

Westerborn [31] attempted to determine how long the renal artery could remain obstructed and resume its function after the reestablishment of circulation. He ligated the renal artery in each of a series of rabbits, observing the renal function later by excretory urographic examination. He also examined the removed kidneys after the death of the animal. When the artery was kept ligated less than eighty minutes the kidney retained its function and its anatomic structure was unchanged. When anemia was of longer duration the function was maintained only in exceptional cases. He found that with the rabbits

31. Westerborn, A.: Embolie in der Arteria renalis mit Bericht über einen operierten Fall, sowie über experimentelle Untersuchungen darüber, wie lange die Blutzufuhr nach der Niere abgesperrt sein kann, ohne dass ihre Funktionsfähigkeit aufgehoben wird, Ztschr. f. Urol. **31**:687-708 (Sept.) 1937.

in which circulation to the kidney was obstructed for over ninety minutes the kidney was destroyed completely.

Westerborn concluded that the same conditions prevail in man and that it may be possible to preserve a human kidney obstructed by embolus, but only if the embolus can be removed within possibly the first hour after obstruction. This time might be extended if the obstruction is not complete. The obstruction probably was not complete in Westerborn's case, in which the crushing of the embolus forty-eight hours after obstruction reestablished temporary renal function.

Pelvic Pain.—The renal pelvis varies so markedly within normal limits that it is difficult to set any normal standards. Notwithstanding this fact, Minder [32] concluded that there is a definite connection between infection, pain and the form of the pelvis. The fact that a renal pelvis is anatomically normal is not proof that its function will be normal. A disturbance of urinary excretion may cause the same amount and type of trouble as are caused by morphologic changes of the renal pelvis. The position of the kidney is of little importance in relation to the situation of pain. Abnormality of the ureteropelvic junction together with infection increases the incidence of pain in the case of any diseased kidney. A low or ptotic kidney should not by itself cause pain.

Renocolic Fistula.—Wesson [33] stated that renocolic fistulas occur secondary to a chronic suppurative renal lesion associated with perinephritis or perinephric abscess. He reported cases; the fourth patient, aged 87, died before any diagnostic procedures could be carried out. In 1 case the fistula passed directly from the bowel through the substance of the kidney to a calix. In the other 2 the opening was in the pelvis and was connected indirectly, through a perinephric abscess, with the bowel. In 1 case the fistula developed nine years before the operation, and the patient's good health during the interim was attributed to the treatment of a nonexistent cancer by means of roentgen therapy. A silent renal staghorn calculus was present in 1 case, but the fistula was caused by a proteus infection.

The morbidity and mortality rate from proteus infection in the genitourinary tract is very high.

Observations on the Capsule.—Rolnick [34] stated that the true capsule acts as a protective barrier to trauma and prevents the spread of infection to the kidney. There is a constant interchange of fluid on the renal surface, which may be of considerable clinical and physiologic

32. Minder, J.: Ueber den Zusammenhang zwischen Nierenschmerz, Beckenform und Infektion, Ztschr. f. Urol. **31**:586-595 (Sept.) 1937.

33. Wesson, M. B.: Renocolic Fistulae: Reports of Three Cases, Tr. Am. A. Genito-Urin. Surgeons **30**:159-167, 1937.

34. Rolnick, H. C.: Some Observations on the Renal Capsule, J. Urol. **38**: 421-426 (Nov.) 1937.

importance. This fluid lubricates the renal surface and allows for the constant finding of a plane of cleavage between the capsule and the kidney. Decapsulation is harmful to the kidney. The new capsule consists of scar tissue only; it does not protect the kidney and may interfere with renal function.

Surgical Technic.—De Vincentiis [35] stated that there is a wide difference of opinion as to the relative advantages of the electric cutting current and those of the scalpel, some writers regarding the cutting current as indispensable in the surgical armamentarium and others considering its use dangerous to any kind of tissue. He decided to carry out research in a series of operations (nephrotomy) in which the cutting current should especially be indicated. Because this procedure so often is followed by hemorrhage, opening the kidney with the cutting current should be particularly advantageous. De Vincentiis performed histologic and functional studies with a series of 36 rabbits, comparing the value of these two methods of cutting.

After use of the cutting current the concentration of urea in the blood rose even more than when the scalpel was used; it remained at the new level for twelve days. In both cases there was increased elimination of urea in the urine.

With reference to histologic studies, wide nephrotomy performed with the scalpel always is attended by hemorrhage, and despite two transcapsular sutures and compression of the renal pedicle 3 rabbits died of hemorrhage on the second day. When the cutting current was used, no incident of this kind occurred. Although macroscopically there was this marked difference in the incidence of hemorrhage, microscopically the hemorrhagic zone, with reference to extension, did not seem to differ in the two types of intervention. The time required for absorption of the blood was sixteen days after the use of the scalpel and twenty-four days after the use of the cutting current.

In addition, the incision with the cutting current is less sharply defined; the margins of the wound are altered and necrotic, and cicatrization is slower. With the scalpel this process was complete on the sixteenth day; with the cutting current it was not complete until thirty days later.

The consideration that merits most attention, however, is the constant and repeated observation with all the histologic sections that in tissues incised with the cutting current there was extensive necrosis of the parenchyma of the kidney whereas in tissues incised with the scalpel there was little necrosis, and that was limited to the region of the incision. In tissues incised with the cutting current this necrosis was

35. de Vincentiis, A.: Nefrotomia col bisturi elettrico e col bisturi commune (ricerche istologiche e funzionali), Arch. ital. di urol. **14**:386-408 (July) 1937.

always wide in extent and was diffused beyond the region of the incision. Moreover, the degenerative processes within the cortex were much more advanced than in tissues incised with the scalpel and consisted of changes which involved indifferently the tubules and the glomeruli. Thus, de Vincentiis concluded that the kidney is extremely sensitive to the electric current. After twenty-four days, and still more completely after one month, the degenerative processes and the zones of necrosis had disappeared from kidneys treated with the scalpel, whereas in kidneys treated with the cutting current degeneration and necrosis were still present, although in less degree, throughout the duration of the observations, which was two months.

Wenzl [36] discussed partial resection of the kidney, which he adopted in 5 cases, with good results in 4. In the other, death occurred from septicemia.

When the kidney is irritated by inflammation and suppuration, the muscular power of the pelvis and ureter is small. It rises spontaneously if the inflammatory foci are eliminated by partial resection or by continuously repeated irrigation through a double-ended nephrostomy tube. A further rise in the muscular power of the uropoietic system can be effected by forcing fluids and by intestinal irrigations with the "enterocleaner." Irrigation acts not only by increasing the amount of fluids excreted through the kidney but by stimulating peristalsis of the excretory urinary system as well. By vigorous contractions the secreted urine is eliminated quickly without leaving residual urine; this hinders the recurrence of urinary calculi.

For prevention of recurrence of formation of stones, the following principles should be observed:

1. Renal stones should be removed before serious infections and degeneration of the kidney have occurred.

2. During operation the pelvis of the kidney should be palpated carefully, and all fragments of stone should be removed.

3. If any infection is present, permanent drainage should be established.

4. In postoperative care, antiseptic washing or treatment with bacteriophage is to be used daily.

URETER

Anatomy.—Gayet [37] stated that although in certain cases the intramural portion of the ureter presents the classic appearance of an ampulla

36. Wenzl, O.: Ueber die Teilresektion der Niere mit Vorschlägen zur Verhinderung des Nierensteinrezidivs, Ztschr. f. urol. Chir. u. Gynäk. **43**:452-475 (Nov. 15) 1937.

37. Gayet, R.: L'uretère intra-mural: Étude anatomo-physiologique. Troubles fonctionnels et leur traitement, J. d'urol. **44**:193-217 (Sept.) 1937.

between two contractions, one at the entrance into the bladder wall and the other at the ostium, there is in reality no true ampulla but rather a zone peculiarly dilatable on account of the multiple folds presented by the mucosa. This is proved by the difficulty encountered in injecting the ampulla with an opaque substance in the living subject as well as in the cadaver.

Ureteral muscular fibers do not end at the wall of the bladder but extend all the way to the valve and come to an end not far from its free border. However, they are slender, and the somewhat transparent valve separating the ureter and the bladder for a few millimeters gives the impression that the two mucosae are almost merged into one. When the valve is short the ureter ends at the point of emergence from the intraparietal tract; but when it is long the dimensions of the ureter are somewhat increased.

The musculature of the intramural portion of the ureter consists of an uninterrupted longitudinal layer following the fibers that come from higher up. This layer becomes individualized, expands and reaches its maximal thickness in the midst of the vesical crossing; then the fibers become thinner and diverge to terminate around the ostium without continuing into the musculature of the bladder, of which they are independent. There is no circular layer suggesting a sphincter. The average circular layer of the pelvic portion ends at the bladder. The few arciform fibers that resemble circular layers are inconstant.

The sheath of the ureter represents the continuation of the external longitudinal layer, which, well individualized in its pelvic portion, lies spread out over the external surface of the bladder, without mingling with the vesical fibers and without continuing at the level of the intramural portion.

The relations of the bladder and the ureter are intimate, but there is no true continuity between the two organs. Each retains its individuality, and the ureteral muscular fibers terminate at the level of the ostium. Connective tissue separates the two musculatures, and no exchange between them can be observed.

Gayet's data agreed with those of Cordier; both found that in the living subject this portion of the ureter cannot be injected or distended with opaque material if it is in a healthy condition. If it is diseased or atonic or if lesions are present in its wall, injection is possible in much more frequent instances; hence, failure to visualize an opaque substance at its level is in favor of its integrity.

The elasticity of the intramural part of the ureter is less than that of the portion above the wall of the bladder but is of good quality in the submucosa, which displays good distensibility. The capacity for dilatation is likewise less than in the portion above. Its sensitivity, on

the other hand, is much greater than elsewhere, owing to the large number of its nerve plexuses and ganglions. Its excitability is also accordingly great. Its contractility is striking, since even if isolated from the bladder and pelvic ureter it possesses autonomous movements. Tonicity reaches its maximum in this zone, as does also rhythm.

The intramural portion of the ureter plays a dual role: dynamic and tonic. The real obstacle to vesicoureteral reflux is found in the intramural portion of the ureter, and the muscle within, which opposes the reflux, is in reality the muscle of the bladder itself.

To functional disturbances of the musculature of the intramural portion of the ureter this structure reacts with anatomic modifications (hypertrophy) and physiologic modifications (hypertonia, to the point of spasm). The results of the latter are supramural retention, without narrowing of the intravesical ureter, due to simple disequilibrium of the habitual conditions of ureteral dynamism.

Functional troubles due to atony of this zone also occur. They may be congenital or acquired. They result in vesicoureteral reflux due to dilatation of the supra-adjacent urinary passages. Acquired atony may be of inflammatory or of nervous origin. Treatment is medical and surgical. Surgical treatment varies according to the case. Cystostomy will ameliorate the graver symptoms of cystitis. In cases of extreme involvement nephroureterectomy may be required, but only exceptionally.

Anomaly.—Lepoutre and Dewailly [38] made a study of extravesical openings of the ureters of women. Such a condition is apparently of more frequent occurrence among women than among men. Disregarding exceptional cases, the ectopic ureter corresponds in about a third of cases to a simple kidney, not double; in the other two-thirds it corresponds to a double kidney one ureter of which opens normally while the other opens into the vulva or the urethra. By Weigert's law, the ectopic ureter, the meatus of which is lower, always corresponds to the uppermost of the two kidneys on the side in question. When such a ureter comes from a simple kidney it is always dilated and its parenchyma is atrophic, a point of great importance from the point of view of treatment, because its function is almost nil. Its lower orifice is narrower than a normal orifice. The ureter is dilated and sinuous as a result of defective evolution and chronic infection.

The cardinal symptom of an abnormal ureteral orifice among women is urinary incontinence, which is present from birth, is continuous and is in no way influenced by the patient's posture. In rare cases, however, this symptom does not exist.

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38. Lepoutre, C., and Dewailly, A.: Les abouchements extra-vésicaux de l'uretère chez la femme, Arch. d. mal. d. reins **10**:551-562 (Nov.) 1936.

Such an abnormal orifice usually opens into the urethra and the vulva; more rarely, it may open into the vagina, and exceptionally, into the uterus or into Gartner's or Müller's duct.

When such an orifice is discovered the first thing to do is to catheterize it. If this procedure elicits liquid the composition of which resembles that of urine, it is probable that the opening is ureteral. Injections of opaque substance may enable the physician to secure a pyelogram of the abnormal ureter (if the latter is capable of being catheterized). Intravenous pyelographic study is seldom of any value. In the great majority of cases the diminutive kidney corresponding to the ectopic ureter will not eliminate the injected substance, for it is functionless; no urographic image will be obtainable.

The most reliable means of learning from which kidney the ectopic ureter proceeds is the retrograde pyelogram revealing the absence of a superior calix on one side alone. Papin attached great significance to this sign. It is not, however, absolute in its value.

The treatment is partial nephrectomy, the extirpation of the small kidney corresponding to the ectopic ureter. Sometimes this cannot be done, and it is necessary to remove the entire kidney on the affected side provided the opposite kidney has good function.

Injury.—The question of transverse suture of the ureter has been the object of experimental and histologic studies repeatedly in the last year. E. Wildbolz and Hryntschak have shown that a cross-cut and resutured ureter is able to function normally and that hydronephrosis will not develop above if the suture has been made properly. Rubritius [39] reviewed a case which led him to the same conclusions. A man aged 26 had a pyelotomy performed to remove an oxalate stone. Six years later the stone recurred, combined with a large degree of hydronephrosis, and during the second operation an almost impermeable stricture at the ureteropelvic junction was observed. Two centimeters of the ureter was resected, and plastic reconstruction of the pelvis was carried out. Only a few interrupted sutures were inserted, and the wound was drained. A catheter was used as a splint, and the urinary stream was not deviated. The result after six months was excellent from both the anatomic and the functional point of view.

Hernia.—Dourmashkin [40] stated that hernia of the ureter is rare. Seventy previous cases were reported, and with the exception of those in which the condition was observed at necropsy the hernias in all cases were discovered at operation. Dourmashkin cited the first case

39. Rubritius, H.: Zur Querresektion des Harnleiters, Ztschr. f. Urol. **31**: 649-652 (Oct.) 1937.

40. Dourmashkin, R. L.: Scrotal Hernia of Ureter, Associated with a Unilateral Fused Kidney: A Case Report, J. Urol. **38**:455-467 (Nov.) 1937.

in which a positive diagnosis was made by retrograde and intravenous pyelographic studies. The condition frequently is associated with vesical hernia. It also is associated in the majority of cases with hernia of preperitoneal fat. The latter may be transilluminated, which may lead to an erroneous diagnosis of a collection of fluid in the scrotal sac.

Ureteroenterostomy.—Smith [41] stated that ureteroenterostomy in selected cases is an operation which does not carry a prohibitive risk. It was successful in 12 of the last 16 cases in which the simple unilateral technic was used. Coffey's technic no. 2 has been abandoned because of the greater mortality it entails. Ureteral drainage as proposed by Coffey should be carried out promptly if severe pyelonephritis develops. The right ureter may be implanted into the cecum if the sigmoid is not available.

Bilharziasis.—Vermooten [42] discussed bilharziasis of the ureter and reported a series of cases illustrating the stage in the progress of urinary bilharziasis at which the urologist is first consulted. This is, as a rule, eight to ten years after the original infestation; rarely are any ova present in the urine.

The diagnosis can be established only by cystoscopic examination. The cystoscopic picture associated with the various manifestations of bilharziasis is generally known. Attention, however, has not been directed toward the roentgenographic appearance of the ureter, which Vermooten [42] regarded as pathognomonic of the disease in its later stages.

In 1930 Harlow and Afifi drew attention to what they described as "cloudy shadows" and calcified demarcations of the bladder and the lower part of the ureter in cases of long-standing bilharziasis. In 1932 Diamantis reported a series of cases of ureteral and vesical calcification in which the condition was due to Bilharzia haematobia. In 1934 Afifi, describing the "roentgenographic manifestations of urinary bilharziasis," again drew attention to the "cloudy shadows" and to the "calcified demarcations" of the bladder and the ureters. Vermooten's experience with the South African type of bilharziasis indicated that the calcified demarcations in the advanced stage of the disease are rather rare, although pathologic changes in the lower part of the ureter associated with normal conditions in the proximal part, as illustrated in the urograms in his reported cases, are seen frequently.

The veins which drain the bladder also drain the pelvic portion of the ureter. From this and from general knowledge of the clinical

41. Smith, G. G.: Recent Experiences with Uretero-Enterostomy, Tr. Am. A. Genito-Urin. Surgeons **30**:343-346, 1937.

42. Vermooten, V.: Bilharziasis of the Ureter and Its Pathognomonic Roentgenographic Appearance, J. Urol. **38**:430-441 (Nov.) 1937.

manifestations of the disease it was assumed that in a very large percentage of instances when the bladder becomes infested with Bilharzia the pelvic portion of the ureter becomes infested also.

Experimentally, Vermooten [42] has been able to show that if the ureterovesical valve is incompetent regurgitation of urine up a normal ureter at the time of urination will not dilate the ureter but that in similar circumstances an infected ureter will dilate and remain dilated.

Vermooten also has shown experimentally that partial ureteral obstruction will cause not only dilatation of the ureter but also definite elongation, which is manifested by tortuosities or kinks of the ureter. This was later shown to be true clinically as well as experimentally. The tortuosities or kinks, strangely enough, always seem to occur in the upper half or the upper two thirds of the ureter. Except in cases of infestation with Bilharzia this appears to be uniformly true. Presumably the pelvic portion of the ureter is far more fixed than is the lumbar portion.

In cases of ureteral bilharziasis, the ova as a rule are found most frequently in the pelvic portion of the ureter, so that when obstruction occurs at the ureterovesical valve the infested portion dilates, and with the dilatation there is elongation, which should take the form of tortuosities or kinks. For mechanical reasons, the intramural portion of the ureter cannot dilate. As ova are deposited all through this region, the lumen of the intramural portion of the ureter naturally becomes narrowed. With increasing obstruction the entire upper portion of the urinary tract eventually will become dilated also.

Vermooten concluded that as bilharziasis is the only disease that affects primarily the pelvic portion of the ureter without affecting the proximal portion, except in rare instances, dilatation and tortuosity of the pelvic portion of the ureter associated with normal conditions in the lumbar portion of the ureter, in the pelvis and in the calices is and should be regarded as pathognomonic of infestation with Bilharzia haematobia.

Megaloureter.—Crabtree [43] stated that a large dilated ureter, termed by Caulk megaloureter, is characterized in its earlier stage by fusiform, atonic distention of the lower third of the ureter with comparatively normal conditions in the renal cortex, the pelvis and the upper portion of the ureter. In the later stages of the condition the process of distention reaches and involves the upper part of the ureter and the pelvis. In the terminal stages, thinning of the cortex and "clubbing" of the calices are characteristic findings. In these stages renal destruction has been accomplished either partially or completely. In cases of

43. Crabtree, E. G.: Plastic Operation for the Relief of Megalo-Ureter, Tr. Am. A. Genito-Urin. Surgeons **30**:323-342, 1937.

megaloureter the problem of management of the condition is primarily one of the efferent, rather than the secretory, integrity of the renal unit. For this reason the preservation of the secretory organ by correction of the abnormality of its conductive channels becomes a tempting problem for the urologist. This is especially so because not only is the histologic picture of the renal parenchyma practically unchanged microscopically from the normal, in cases in which no infection is present, but the total amount of renal substance which is found above such megaloureters is often about equal to that of the uninvolved kidney on the opposite side, and its secretive ability remains unimpaired for many years.

Megaloureter may be unilateral but is often bilateral. In 2 of Crabtree's cases it was associated with the lone kidney in patients with congenital absence of the other kidney. Infection was absent in only 3 of the cases which he has observed.

Five causes of megaloureter have been recognized. These are obstructions external to the bladder, ureteral stricture of the ureterovesical region, ureterocele, absence of the ureterovesical valve and neurogenic disturbances of the ureter.

The megaloureter is a changed ureter and is considered the end result of three factors: hypertrophy of the musculature of its walls, decompensation after the peak of hypertrophy has been passed and fixation caused chiefly by fibrosis and hyperplasia of the mucosa.

A survey of the literature indicates that four types of treatment have been employed for megaloureter, in addition to the obvious one of correction of pathologic changes in the urethra and the neck of the bladder. They are ureteral dilation, enlargement of the ureteral orifice by surgical operation, ureteral resection by the method of Hinman and ureteronephrectomy.

Ureteral dilation is adequate to produce great improvement in some cases of less extensively changed ureters. It cannot always be done; it is sometimes impossible either to catheterize the orifice or to produce lasting benefit even if dilation is accomplished, because dilation of some strictures produces only fracture of the walls of the stricture.

Various methods of enlarging the orifice in cases of congenital narrowing of the ureterovesical juncture have been devised. The most widely employed method is section of the orifice through the vesical wall and the nearby ureteral wall, after which the mucous membrane of the ureter is sutured to the mucous membrane of the bladder.

Hinman has contributed toward eliminating longitudinal redundancy of the megaloureter as well as toward correction of the ureterovesical defect but has not considered lateral redundancy. He has freed the ureter from the bladder, after which, either by dilatation of the orifice through the vesical wall for reinsertion of the ureter or by creation of

a new vesical opening, he has drawn the ureter through the vesical wall. The excess length of ureter then has been excised and the stump of the ureter anchored to the bladder. He has also resected at other points in the course of the ureter.

Most observers have agreed that if the disease is unilateral and the condition of the other kidney is normal, ureteronephrectomy is the operation of choice.

Crabtree [43] presented the results of plastic operations on megaloureter in which attention was paid to elimination of both longitudinal and lateral redundancy of the ureter in one instance and elimination of lateral redundancy alone in the other. These operations were performed in 2 of the 3 cases of megaloureter without infection which he has encountered. In the first case end results have been observed after ten years; in the second, after one year. In the first instance nephrectomy was refused by the patient. In the second case the condition occurred in association with a lone kidney.

In the first case the kidney was extensively diseased prior to operation. The kidney was cleared of its infection spontaneously and at the end of ten years had sufficient function to fill by the intravenous method within the average filling time for the normal kidney.

In the second case the kidney improved in function, lent itself to elimination of infection by antisepsis and showed reduction of the combined ureteral and pelvic capacity to 14 cc.

Vermooten [44] in discussing megaloureter stated that Chwalla restudied the embryology and the development of the human cloaca and the urogenital sinus, including the early development of the ureter. He found that there was a complete diaphragm across the lower end of each ureter in embryos of approximately the 10 to 20 mm. stage and occasionally in older ones. The diaphragm was composed of only 2 layers of cells. On the one side these resembled vesical epithelium and on the other ureteral epithelium.

Vermooten has investigated a large series of roentgenograms of dilated ureters of children. In many he saw a definite obstruction or a valvelike formation in the region in which the ureter enters the bladder. Such a band or diaphragm may be seen a little above the ureterovesical orifice. For that reason it is conceivable that surgical dilation of the ureter may not completely destroy or remove the remnants of Chwalla's membrane. Relatively little relief, therefore, will be had from the obstruction. This condition, of course, is an expression of the existence of such conditions as ureterocele, diverticulum and other similar congenital anomalies in the region of the ureterovesical orifice.

44. Vermooten, in discussion on MacKenzie, D. W., and Seng, M. I.: Obliteration of a Ureter in an Anomalous Kidney with Hydronephrosis, Tr. Am. A. Genito-Urin. Surgeons **30**:347-363, 1937.

PROSTATE

Hypertrophy.—Hinman [45] stated that the operation of perineal prostatectomy for hyperplasia of the prostate gland is safe. The modern method of hemostasis and plastic closure controls hemorrhage and shortens the patient's stay in the hospital by half. The functional results are as good as those achieved by any other method, if not better; and they are of equal permanence. Injury to the rectum with the formation of fecal fistula, the only actual disadvantage, is rare. The majority of such fistulas close spontaneously, and the few which do not can be closed surgically with very little risk.

The greatest advantage of the perineal operation over all others used in the treatment of hyperplasia of the prostate gland lies in the relation of hyperplasia to cancer. Cancer of the prostate gland is frequent, occurring in 14 of every 100 men more than 45 years of age. More than 1 of every 5 men who have prostatism have cancer. More than half the patients who have cancer also have hyperplasia of the prostate. Although the two lesions are distinct, any method of treatment of hyperplasia which neglects the possibility of cancer is not a good method. The perineal route is the only one by which both hyperplasia and cancer can be approached successfully at the same time. It is the only route by which a suspicion of cancer can be confirmed and by which operation best suited to all the conditions found can be carried on satisfactorily. The perineal route is the only approach by which radical removal of cancer of the prostate gland unassociated with hyperplasia can be performed with preservation of normal micturition.

Uhle and Melvin [46] reported a case with two recurrences of benign prostatic hypertrophy or tertiary prostatic hypertrophy.

The incidence of recurrence varies between 1 and 2 per cent. In a recent review of 227 cases of benign prostatic enlargement in which operation was done by either the suprapubic or the perineal route at the hospital of the University of Pennsylvania between the years 1923 and 1932, 3 recurrences (1.3 per cent) were observed, including that in the case reported by Uhle and Melvin.[46]

The surgical pathologic picture of benign prostatic enlargement precludes the removal of the prostate gland at operation. Adenomatous tissue is enucleated. Adenoma, during its period of growth, expands and compresses prostatic tissue into a thin shell resembling a capsule. To distinguish this from the true capsule of the prostate anatomists have called it the surgical or false capsule. With pressure removed, the

45. Hinman, F.: The Modern Operation of Plastic Perineal Prostatectomy, Tr. Am. A. Genito-Urin. Surgeons **30**:265-274, 1937.

46. Uhle, C. A. W., and Melvin, P. D.: Tertiary Prostatic Hypertrophy: An Unusual Case Report, J. Urol. **38**:487-493 (Nov.) 1937.

prostatic tissue either remains atrophic or regenerates to resume its normal size. Therefore it seems logical to assume that the same cause which produces the original growth may produce the recurrence. Another factor in recurrence, and one that has received theoretical consideration from various authors, is the failure, at the first operation, to notice small spheroids of adenomatous tissue, or the incomplete removal of such processes. If the blood supply is not injured, these small spheroids are capable of regeneration to such an extent that they may interfere with the dynamics of micturition.

Brucella Infection.—Boyd [47] reported the discovery by culture of Brucella abortus in the prostate gland of a patient with chronic brucellosis. The diagnosis of brucellosis was not made until the bacteria were found in the prostate gland. The patient had been sick for years with symptoms of varying intensity and was sometimes bedridden. Examinations at some of the best clinics in America and by some of the best internists failed to disclose the cause of the illness. Cultures were made from the prostate gland because of the persistence of small groups of pus cells and small groups of fine gram-negative bacilli in the prostatic secretion.

Boyd concluded that urogenital infections from which Br. abortus can be cultured are more frequent than is now suspected. Because the diagnosis of chronic brucellosis is often so difficult, cultures of material from the urogenital organs seem quite worth while when the presence of this condition is suspected. Special technic is required for obtaining growths of Br. abortus in culture mediums.

Echinococcus Cysts.—Liakhovitzky [48] reported a case of primary hydatid cyst of the prostate gland. This condition is rare. In the Russian literature he has found records of only 7 authentic cases; in an equal number of others there were lesions which proved to be retrovesical cysts. The patient was a man aged 25 who was admitted to the oncologic dispensary for sarcoma of the prostate gland. Examination of smears of the blood revealed 7 per cent eosinophils. The results of the various investigations led to a diagnosis of hydatid cyst of the prostate gland. Operation was performed. There are five ways in which such a cyst may be approached: (1) by the extraperitoneal route, through the abdominal integuments; (2) by the perineal route; (3) by incision of the abdominal integuments combined with perineal section; (4) by the transvesical route, and (5) by the transrectal route.

47. Boyd, M. L.: Human Prostatic Infection with Brucella Abortus (Alcaligenes Abortus), Tr. Am. A. Genito-Urin. Surgeons **30**:259-264, 1937.

48. Liakhovitzky, M.: Kyste hydatique de la prostate, J. d'urol. **44**:398-402 (Nov.) 1937.

The first of these was chosen. The tumor was smooth and as large as two fists. After puncture, which elicited a clear fluid, the anterior wall of the tumor was sutured to the edge of the cutaneous wound. When the cyst was opened a large amount of yellow-amber fluid escaped. The chitinous tunic was extracted in a single piece. The cyst was cleansed and drained, and a tampon was inserted. During the first month thereafter, the cavity secreted 10 to 14 cc. of fluid. Secondary hydatids were observed on several occasions and were evacuated. After eight months in the hospital the patient was discharged, at which time he had a small fistula which closed one month later. He was in good general condition and complained only of a diminution in sexual potency.

In most cases reported the clinical picture was that of compression of the urethra as well as of the rectum, the latter symptom predominating. In this case, as in others, the patient had suffered from pain in the anal region and from dysuria and pollakiuria. Except during defecation and urination, the pain had not been acute; the discomfort was more like a sense of heaviness from the pressure of a weight.

The cystoscopic picture is characteristic, showing the rounded form of the grayish red or grayish blue cyst. A transparency is seen near the free border of the tumor, and blood vessels traverse the cystic surface. In the eight operations that have been done in Russia, the transvesical route was used six times; the perineal, once, and the extraperitoneal through the abdominal wall, once. As to the mode by which the scolices penetrate the prostate gland to produce primary hydatid cyst, the possibility of their arrival through the blood stream must be excluded entirely; so the only possible way is by direct penetration of the rectal wall.

BLADDER

Tumor.—Higgins [49] stated that cystectomy and transplantation of the ureters had been performed in 34 of his cases of carcinoma of the bladder. A reduction in the mortality was obtained by performing the operation before dilatation of the ureters, renal infection and impairment of renal function had occurred. Less radical operative procedures should be employed in cases of advanced carcinoma of the bladder associated with dilatation of the ureters, pyelonephritis and impaired renal function. Such vesical carcinomas lie beyond the range of operability with this type of surgical procedure.

Patients who survive the operation (and the percentage of such patients is gradually increasing) have satisfactory control of the urine; they may return to their social and business activities in comfort.

49. Higgins, C. C.: Cystectomy and Transplantation of the Ureters into the Bowel for Carcinoma of the Bladder, Surg., Gynec. & Obst. **66**:549-556 (Feb. 15) 1938.

Insufficient time had elapsed to warrant statements as to the percentage of five year cures. The immediate results, however, were gratifying, and Higgins concluded that the outlook is optimistic.

Graves and Dresser [50] have studied the routine records of 24 patients with cancer of the bladder who were given external irradiation as the first direct treatment of their disease.

The average age of these patients was 67.6 years. Nine of them were more than 70 years of age. Most of the tumors were moderately advanced or were extensive. Fifteen were classified clinically as operable; 9 were called inoperable. Most of the tumors involved the region of the trigon of the bladder or were in close proximity thereto. In 12 cases the lesions were recorded as multiple.

Even with a relatively low dosage and with no great emphasis on the method, high voltage roentgen therapy is said to have resulted, temporarily at least, in arrest of hematuria in more than half of our cases. There was gross evidence of some degree of regression, great or slight, in at least half the cases; there was no such evidence in 6 cases, and of 4 cases no record was kept. There was an occasional instance in which it was felt that the amount of regression was sufficient to classify the patient more definitely with the group whose tumors were considered operable.

Some form of operation was deemed necessary, and was employed in 17 cases at varying intervals after high voltage roentgen therapy. The procedures were as follows: suprapubic cystotomy, electrocoagulation and implantation of radium, 10 cases; cystoscopic fulguration and implantation of radon seeds, 4 cases; resection of the anterosuperior portion of the bladder, 1 case; total cystectomy, 1 case, and suprapubic cystotomy, electrocoagulation and packing of the bladder for the emergency control of hemorrhage, 1 case.

Graves and Dresser [50] were aware of no increased technical difficulty at the time of operation because of the previous administration of external irradiation but it was their distinct impression that wounds healed more slowly and were more involved in infection and that the convalescence of the patients was longer and more difficult than in cases in which high voltage roentgen therapy had not been employed as a preoperative measure.

In conclusion, as a result of their study, Graves and Dresser [50] stated that external irradiation with 200 kilovolt equipment by ordinary methods and with ordinary dosage has no place as a curative agent in the routine treatment of malignant tumors of the urinary bladder. As a

50. Graves, R. C., and Dresser, R.: Experiences with High Voltage Roentgen Therapy in the Treatment of Malignant Tumors of the Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **30**:201-207, 1937.

palliative agent it is useful, especially in the arrest of hemorrhage, and in an occasional case sufficient regression may be accomplished thereby to render an extensive lesion more amenable to cure by other means.

Tumors which are amenable to cure by operation or by operative treatment combined with interstitial radiation are still best treated by these means. Apart from its important role as a palliative agent in cases of inoperable tumor, the greatest promise for the usefulness of high voltage roentgen therapy lies in the treatment of radiosensitive types of multiple papillomatosis of the bladder and in the treatment of those conditions, also radiosensitive, in which the tumor has involved both ureters or the region of the vesical neck.

Barringer [51] in a report on radium therapy in 215 cases of carcinoma of the bladder stated that his three year cures were obtained by use of radium in 69 cases, or 32 per cent. Five year cures occurred in 52 cases, or 24.1 per cent (a drop of 7.6 per cent). The total number of cases in which the bladder became free of cancer was 96, or 44.6 per cent. Treatment in these cases was by cystoscope and by suprapubic implantation. They include all cases in which the bladder was opened, no matter how extensive the disease. In many cases of extensive carcinoma, radium was implanted with the idea of controlling metastasis. Notwithstanding this, five year cures fail in about three fourths of all cases.

The factors influencing physicians' choice of therapy are the size, grade and position of the tumor and the condition of the kidneys. Small tumors, papillary or infiltrating, are best treated cystoscopically, either by implantation of radon seeds or by applications of radon. Large tumors, if papillary, are treated by suprapubic implantation of radon. Large tumors, if infiltrating, are treated by methods to be outlined. Tumors of lower grades of malignancy are treated as has been outlined. Tumors of higher grades of malignancy, particularly those of grade 4, are treated if possible by external irradiation and cystoscopically. When a tumor is on the base of the bladder (as are 75 per cent of all vesical tumors), encroaching on the ureters or internal urethra, irradiation therapy is superior to operative removal.

If the kidneys are infected and the ureters and renal pelvis dilated, cystoscopic treatment by radium is superior to the open operation. The suprapubic operation and the massive implantation of radon seeds add to the infection. The implantation or application of radium cystoscopically can be performed in divided treatments.

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51. Barringer, B. S.: Radium Therapy of Bladder Carcinoma: Five-Year Results; Failures; Future Therapy, Tr. Am. A. Genito-Urin. Surgeons **30**:209-214, 1937.

One of the disadvantages of radium treatment is that the implantation of seeds into an infected tumor increases the amount of infection present. A slough always is formed, and this presents a focus of increased infection. The slough may become incrusted with calcareous deposits, and stones may form as a result. Asepsis and a certain amount of antisepsis help to obviate this condition. Cleansing of the bladder with antiseptic washes before and after cystoscopic implantation, extreme care in the suprapubic approach and painting of the tumor with mild solutions of iodine before implantation of radium are all helpful.

Vesicovaginal fistulas occur as the result either of implantation of radon or of the depth of the tumor, or both. Barringer [51] had 3 cases of such fistulas. Not only the size of the tumor but the degree of infection and the condition of the kidneys should determine whether the method of treatment is to be suprapubic or cystoscopic. Barringer concluded that the cystoscopic treatment is preferable. If the tumor is ulcerated and infected and if one or both of the kidneys are hydronephrotic, suprapubic implantation of a large amount of radon is a dangerous procedure from the standpoint of infection.

The forms of radiation in use include radon seeds; roentgen therapy alone or combined with the use of radon seeds; fulguration and roentgen therapy combined; preoperative and postoperative roentgen therapy, and application of radium. Radon seeds have constituted the best medium for both suprapubic and cystoscopic application of radium. Notwithstanding repeated and persistent attempts to control the more intractable types of cancer of the bladder, high voltage roentgen therapy alone has failed signally. The use of roentgen therapy in the cases of mild cancer of the bladder or of papilloma, which could easily be controlled by cystoscopic fulguration or by application of radium, is unjustifiable, according to Barringer. Barringer has attempted in 3 cases of ulcerated extensive infiltrating carcinoma to combine the use of roentgen therapy and the use of radon seeds. The radium was applied either cystoscopically or suprapubically. All 3 patients succumbed. Considerable work has been done lately with the instrument used for transurethral prostatectomy for fulgurating extensive tumors of the bladder; this was followed by the use of roentgen therapy. No extensive series, according to Barringer, have been reported. It seems that fulguration as an adjunct to roentgen therapy is not as effective as radium.

It would seem thoretically that either preoperative or postoperative roentgen radiation might partially devitalize tumor cells so that operative removal would result in a larger number of cures. Barringer concluded that this is more a theoretic than a practical consideration. The

application of a large amount of radium held against a tumor for periods of one hour by means of the cystoscope under direct vision might seem to offer a chance of controlling a large ulcerating cancer of the bladder. These treatments are supplemented by high voltage roentgen therapy. Barringer [51] had several cases in which this method was used and was effective.

Keyes [52] reported a series of 31 cases in which the patients were observed ten to eleven years after suprapubic implantation of radon seeds into epithelial tumors of the bladder too extensive for control by cystoscope.

Prompt control of recurrences prevents increase in malignancy. Ten cases of grade 1 and grade 2 tumors were reported. In half these cases the tumor recurred, and in 2 cases the patients died of the disease. Yet, thanks to routine cystoscopic studies, half of these patients have been free of tumor for a number of years, and in 2 others the condition has been controlled by cystoscopic observation during the ten years in which the tumors have continued to recur. Tumors of grades 3 and 4 show much less tendency to recur; if not palpably infiltrating they may be controlled in the majority of cases. Of 6 patients, 4 were free of tumor when last seen or heard from, a number of years after operation.

Infiltration palpable on preoperative rectal or abdominal examination is a sign that the tumor is incurable. In this series only 1 such tumor was controlled. Three of the patients died of cancer of the prostate gland. Although necropsy was not performed, the cancer in 1 case was believed to be secondary to a tumor of the bladder or of the urethra.

Deming [53] described a new surgical approach for treatment of carcinoma of the neck of the bladder. A patient who had cancer of the vesical neck and was treated with radical perineal excision of the vesical neck, part of the trigon, the prostate gland and seminal vesicles was reported well after a period of six years. Restoration of normal urination was secured. The comfort of the patient after this operation was extraordinary as compared with the discomfort of the long period during which the patient usually suffers from dysuria after treatment with radium. The technic of the operation is not difficult. Total cystectomy with transplantation of the ureters is not necessary for certain types of cancer which develop at the vesical neck. Radical perineal resection of the vesical neck and the prostate gland for cancer of the vesical neck should be employed more often than has been customary.

52. Keyes, E. L.: Thirty-One Patients with Bladder Tumor Treated Ten Years Ago by Suprapubic Section and Radon Implantation, Tr. Am. A. Genito-Urin. Surgeons **30**:215-221, 1937.

53. Deming, C. L.: Successful Radical Perineal Resection of Bladder Neck for Carcinoma, Tr. Am. A. Genito-Urin. Surgeons **30**:227-234, 1937.

Smith [54] in discussing tumors of the bladder stated that the single or perhaps double small pedunculated tumor, whether it is papillary carcinoma of low grade or frank papilloma, can be successfully treated by excision cystoscopically or suprapubically, with the implantation of one, two or three radon seeds beneath the pedicle of the tumor.

When such pedunculated tumors occur in greater numbers than two it is usually necessary to open the bladder suprapubically so that thorough access may be obtained, but the same process can be employed. In treatment of this type of tumor Smith stated that thorough electrocoagulation of the stump is of value.

With the single, infiltrating tumor the situation is a little different. In Smith's experience electrocoagulation, although temporarily successful, has not produced good permanent results with this type of tumor. Either the entire thickness of the vesical wall should be resected, if that is feasible, or radium should be implanted beneath and about the infiltrated portion of the wall of the bladder, well outside the region of palpable induration.

Dermoid Cyst.—Shih and Char [55] reported the occurrence of a dermoid cyst which had ruptured into the urinary bladder.

Symptoms of this condition usually make their appearance at some time between puberty and old age and may be in no way distinctive until rupture into the urinary bladder has occurred. The cysts always contain hair, and the passing of hair in the urine, pilimiction, constitutes a major symptom. Calculous incrustations frequently form around hairs as nuclei, and the passing of stones, teeth and sebaceous material has been observed. Rupture always is followed by complicating cystitis.

Excision of the dermoid cyst is the logical procedure. When it is impossible to dissect the cyst from the urinary bladder, it may be necessary to resect a portion of the vesical wall. Postoperative care consists of drainage of the urine by means of an indwelling urethral catheter, which allows the vesical wound to heal without tension.

Diverticulum.—In the course of removal of a diverticulum of the bladder after sudden collapse of the patient, Hryntschak [56] merely severed the diverticulum from the bladder and inserted a drain into the diverticulum.

The postoperative course was astonishing. The patient recovered readily; the drain was removed on the thirteenth day, and there were

54. Smith, G. G., in discussion on Cabot, H., and Pace, J. M.: Methods of Selecting the Proper Operative Treatment for Cancer of the Bladder, Tr. Am. A. Genito-Urin. Surgeons **30**:235-258, 1937.

55. Shih, H. E., and Char, G. Y.: Dermoid Cyst Ruptured into Urinary Bladder, J. Urol. **38**:165-172 (Aug.) 1937.

56. Hryntschak, T.: Zur operativen Behandlung des primären Blasendivertikels, Ztschr. f. Urol. **31**:659-663 (Oct.) 1937.

no further symptoms from the diverticulum. The prostate gland, which was enlarged, was removed two months afterward by transurethral resection. Searching the literature, Hryntschak found that in a few cases the condition had been treated in the same manner and with good results; always, as in his case, the operation had been done as a makeshift procedure.

The excellent result obtained in his case by exclusion and drainage of the diverticulum combined with transurethral resection of the vesical neck convinced him that this is the best method of procedure in similar cases.

Injury.—Stevens and Delzell [57] stated that rupture of the bladder is to be distinguished from perforation. The mortality from the former is higher than that from the latter. Twenty-seven cases of all types of vesical injury involving rupture or perforation are reported. Eight of 14 patients who had intraperitoneal injury died, but death occurred in only 2 of 13 patients who had extraperitoneal injury alone.

Roentgenographic methods are theoretically preferable in arriving at a diagnosis, but cystoscopic study has been applied more readily, and it has given a positive diagnosis in nearly 85 per cent of cases. If operation is performed promptly, we doubt whether it adds to the risk. Diagnosis by catheter is notoriously unreliable. The treatment is to operate promptly and to establish efficient drainage of the site of injury and of the bladder. Stevens and Delzell [57] preferred suture of the traumatic opening, but this is not always essential. Exploratory laparotomy is important, especially in the early stages. Transfusion or treatment of shock may be required before operation can be considered.

Exclusion.—Henry Wade [58] reviewed his 60 cases of exclusion of the bladder by diversion of the urinary stream, into the colon in 54 cases, to the surface of the skin in 5 and into a fistula in 1. He concluded that the Coffey-Mayo technic or Coffey's technic no. 1 is the best and that technics no. 2 (tube technic) and no. 3 (transfixion suture) are unsound in principle and inferior in many ways to no. 1. Since 1934 he has performed bilateral simultaneous implantation made possible by immediate intravenous infusion of sodium sulfate solution as advocated by I. L. Dick. This promotes renal secretion and prevents anuria. In the 54 cases of transplantation to the bowel, 36 transplantations have been bilateral and simultaneous, without the use of catheters. Ten additional transplantations have been done for patients who had single kidneys.

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57. Stevens, A. R., and Delzell, W. R.: Traumatic Injuries of the Bladder, with Report of Twenty-Seven Patients Operated Upon, Tr. Am. A. Genito-Urin. Surgeons **30**:185-196, 1937.

58. Wade, H.: Vesical Exclusion, Proc. Roy. Soc. Med. **31**:277-292 (Jan.) 1938.

Indications for this operation, according to Wade, are congenital malformations, such as complete exstrophy and subsymphysial exstrophy or epispadias among women, vesicovaginal fistula, vesical carcinoma, carcinoma of the cervix uteri treated with radium and followed by vesicovaginal fistula, tuberculous cystitis, interstitial cystitis, urethral stricture with urethral and vesical fistulas and spina bifida with vesical incontinence. Careful preoperative study and preparation are important. Examination by excretory urographic study is essential. The bowel is prepared carefully, and the preliminary use of scopolamine and morphine together with spinal anesthesia provides good relaxation and contraction of the colon. Clamps are not used, and Wade did not approve of any cleansing or packing of the bowel.

The mortality rate in cases of carcinoma of the bladder in which this operation is used is high (51 per cent in Wade's hands, as compared with 25 per cent for nonmalignant conditions). Since January 1936, in a total of 25 cases the mortality has been reduced to 43 per cent for carcinoma and to 9 per cent for nonmalignant conditions. If operation is survived, the danger of ascending renal infection and suppurative pyelonephritis is slight, and with nonmalignant conditions the expectancy of life for the patient is reduced little if at all. A normal, useful and contented life is made possible despite the profound physiologic alteration brought about by surgical intervention.

Function.—After a study of the literature and of his own cases of disturbed vesical function in cases of cerebral disease, Schubert [59] reached the following conclusions: There are cortical and subcortical vesical centers in the brain. The cortical center lies bilaterally in the lobulus paracentralis near the center which controls the foot. Its fibers run with the pyramidal fibers toward the spinal cord. The subcortical center lies on both sides of the third ventricle in the hypothalamus and can act independently on the bladder. There are probably no vesical centers in the cerebellum. The type of vesical dysfunction (incontinence or retention) is independent of the seat of the lesion; the duration is longer in cases of bilateral cerebral lesions. The cause of the cerebral lesions may be trauma, tumor or apoplexy or, more rarely, chronic degenerative and inflammatory processes.

Reconstruction.—Gironcoli [60] attempted the construction of a new bladder from the cecum in 4 cases of carcinoma of the bladder. His experience was discouraging. Three patients died after the operation; the fourth enjoyed five years of good health and then died from uremia

59. Schubert, H. O.: Ueber Blasenstörungen bei cerebralen Erkrankungen, Ztschr. f. urol. Chir. u. Gynäk. **43**:527-539 (Dec. 22) 1937.

60. de Gironcoli, F.: Ueber die kontinente Darmblase, Ztschr. f. Urol. **31**: 652-658 (Oct.) 1937.

caused by ascending urinary infection. Gironcoli, in discussing his experience, stated:

> The construction of an intestinal bladder is a serious operation, serious in itself and the more so because it is done usually on cachectic patients. To reduce risk, the operation is done in stages. By this method of multiple operation, much time is lost and the patients suffering from carcinoma of the bladder become more and more cachectic, as they derive no benefit from the preparatory operations. Even when a well functioning intestinal bladder is constructed, the patient may die from infection of the urinary tract.

URETHRA

Tumor.—Mortensen [61] reported a case of carcinoma of the male urethra. The rarity of the condition, coupled with the inaccessibility of the usual site of its occurrence, that is, the bulbous urethra, renders early diagnosis extremely difficult. In addition, the lesion almost invariably is grafted on some more chronic and more frequent lesion in this situation.

Histologically, carcinoma of the urethra must be distinguished carefully from carcinoma arising in the penis, the prostate gland or Cowper's gland and also from secondary involvement of the urethra from these regions. A large percentage of urethral carcinomas are of the squamous cell type, the occurrence of which in a site normally lined by transitional epithelium is explained by the process of epithelial metaplasia. The frequent occurrence of pathologic changes in epithelium leading to the development of leukoplakia, discovered in routine urethroscopic examination for the diagnosis and treatment of chronic urethral infections, stresses the importance of this factor. The papillary type of tumor is found less frequently; it is often observed in younger patients, with whom it is of more rapid growth and of greater malignancy. True adenocarcinoma of the urethra has been described on only 2 occasions. It arises from the glandular structures of the urethra.

In most cases the results of treatment are poor, and in by far the greater number of cases reported the patient has died shortly after diagnosis has been made, whether or not surgical intervention was employed.

Harbach [62] stated that primary carcinoma of the male urethra is of a low degree of malignancy, is slow to metastasize and, owing to its situation, is particularly suitable for resection. It is apparently a disease of middle age, although Paton reported its occurrence in a youth aged 18 and Kroiss in a man aged 91. The chief difficulty is in diagnosis, and

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61. Mortensen, H.: Carcinoma of the Male Urethra, with Report of a Case, Brit. J. Surg. **24**:669-675 (April) 1937.

62. Harbach, F. O.: Primary Carcinoma of the Male Urethra, J. Urol. **38**: 311-315 (Sept.) 1937.

in practically all cases the diagnosis has been made late, often too late for any hope of cure. The rarity of the disease is proved by the fact that in the past hundred years only about 100 cases have been reported.

The majority of patients have a history of some form of chronic urethral irritation. A history of trauma is frequent. Rizzi in a study of 52 cases found a history of gonorrhea in 60 per cent and a history of trauma in 10 per cent. Trauma and long-continued chronic urethral irritation must be considered etiologic factors. The growth appears most often in the perineal or membranous portion of the urethra and much more rarely in the penile portion. Legueu cited the incidence as 63 per cent in the perineal portion of the urethra. The symptoms are those of pathologic change in the lower part of the urinary tract. Every case of urethral fistula and stricture should be regarded as a potential case of urethral carcinoma.

Operation offers the best chance of cure. If the growth is situated in the penile portion, partial amputation may be done with success, but one must be certain that carcinomatous cells have not been carried posteriorly by the instruments. The presence of tumor in the membranous urethra necessitates complete amputation with transplantation of the urethra. Complete emasculation is not only unnecessary but mutilating. The inguinal nodes should be dissected, but Harbach stated that this procedure should be carried out after a period of rest following amputation of the penis. Infection and sloughing of the inguinal incisions are more likely to occur when amputation and dissection of the nodes are performed simultaneously.

Kreutzmann and Colloff [63] stated that primary carcinoma of the male urethra is a rare disease, only 145 cases, including the 2 which they observed, having been reported.

The treatment which has given the greatest number of cures of carcinoma involving the anterior portion of the urethra is partial or complete amputation of the penis. When the malignant process involved the posterior portion the best results were obtained by resection of the urethra with the growth included. Inguinal adenectomy is advisable in all cases.

Catheterization of the Ejaculatory Ducts.—De Assis [64] stated his view on the value of catheterization of the ejaculatory ducts on the basis of 100 cases in which this was done. The procedure is nearly always possible with the help of the new special instruments. Like ureteral catheterization, catheterization of the ejaculatory ducts gives valuable

63. Kreutzmann, H. A. R., and Colloff, B.: The Treatment of Primary Carcinoma of the Male Urethra, J. A. M. A. **110**:184-187 (Jan. 15) 1938.

64. de Assis, S.: Klinische Beobachtungen der Samenblase und Samenwege durch den Katheterismus der Ducti ejaculatorii, Ztschr. f. urol. Chir. u. Gynäk. **43**:427-451 (Nov. 15) 1937.

information. It is as well fitted for diagnostic and roentgenologic purposes as for therapeutic injections. Of the utmost importance is the systematic study of the seminal vesicles, filled with a contrast medium, before fluoroscopic examination is performed. Such observations indicate whether clinical healing is taking place or whether surgical intervention is necessary.

PENIS

Erythroplasia.—Dean and Farrow [65] stated that erythroplasia of the penis is a form of erythematous dermatosis which affects the glans and the mucous surface of the prepuce. It is likely that the condition is the result of chronic irritation beneath a tight prepuce. Although the subjective symptoms are usually mild and the lesions appear insignificant, carcinomatous degeneration has been noted in about 40 per cent of reported cases. The microscopic picture is that of chronic inflammatory precancerous dermatosis. The clinical course is characterized by slow but steady extension and by a complete lack of favorable response to treatment with any topical application. In the case reported intense surface irradiation after circumcision was followed by healing. No evidence of relapse was present after more than a year.

Plastic Restoration.—Brown [66] reported 4 cases of restoration of the entire skin of the penis. In 3 of the 4 instances, free thick split skin grafts gave permanent healing with complete normal sensation and function. In the fourth case, split grafts were used to supplement scrotal flaps and to repair the defect of the scrotum.

In preparing for the graft the superficial granulation tissue and deep scar tissue are carefully dissected away in layers until the penis can be elongated completely, extreme care being used not to enter either the corpora cavernosa or the urethra. The next most important step is to obtain a free thick split skin graft, of about one-half to three-fourths the thickness of the skin of the thigh, in one piece, large enough to cover the penis completely without the necessity of patching. A catheter is inserted, and an assistant holds the penis completely extended on the catheter. The graft is wrapped carefully and smoothly around the penis, the edges being overlapped to assure complete coverage. It is then sewed accurately in place all around the penis, at the corona and at the abdomen, and then down the line of the overlapping edges, with fine horsehair on fine needles. Fine mesh gauze is wrapped smoothly around the extended penis; a gauze flap is then wrapped securely on with a sterile bandage, so that the penis is held in complete extension on the catheter.

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65. Dean, A. L., Jr., and Farrow, J. H.: Erythroplasia of the Penis, Tr. Am. A. Genito-Urin. Surgeons **30**:405-416, 1937.

66. Brown, J. B.: Restoration of the Entire Skin of the Penis, Surg., Gynec. & Obst. **65**:362-365 (Sept.) 1937.

The dressing is kept moist with saline solution added through an irrigation tube and is carefully taken off after four or five days. All sutures are removed, dead edges are trimmed away and any blisters or infected regions are opened.

TESTICLE

Tumors.—Hertzog [67] reported 2 cases of rhabdomyosarcoma of the testis, one of the rarest types of intrascrotal neoplasm. The first case was that of a farmer, aged 35, who had a history of injury to the scrotum in 1921. In 1922 he noticed a small lump in the region of the left testis. This did not increase in size until 1935, when it started to grow gradually. The tumor was removed in 1936, at which time it weighed 1,220 Gm. and measured 17 by 11 by 10 cm. No remnant of the testis or epididymis could be found. The tumor felt firm, but on section a large cystic region was seen, filled with necrotic material. The remaining structure suggested sarcoma. A small portion of differentiated cartilage was present. Microscopic study revealed a tumor composed of striated muscle.

The second case was that of a boy aged 16 who first noticed a slight swelling of the left testis in March 1935. In April 1936 the tumor was removed, at which time it weighed 1,560 Gm. The epididymis could not be found; however, a normal-appearing testis was present. It was entirely surrounded but not invaded by the tumor. No cartilage was present. Microscopically, the tumor was similar to that in the previous case.

Atrophy.—Higgins and Cragg [68] exposed white male rats to fumes of carbon tetrachloride for a brief time each day for periods varying from six to twelve weeks. The animals were then examined, and among the changes found was uniform atrophy of the testes and the accessory sex glands, in contrast to uniform enlargement of the adrenal glands. The authors did not endeavor to interpret the significance of these observations.

TUMORS OF THE UROGENITAL TRACT

Campbell [69] reported on primary malignant tumors of the urogenital tract; the report was based on the clinical and pathologic study in 77 cases of primary malignant urologic disease, the patients being infants and children whose ages ranged from 3 days to 9 years.

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67. Hertzog, A. J.: Rhabdomyosarcoma of the Testis: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **12**:570-571 (Sept. 8) 1937.

68. Higgins, G. M., and Cragg, R. W.: Atrophy of the Genitalia and Hyperplasia of the Adrenal Glands of Rats After Breathing Carbon Tetrachloride, Proc. Staff Meet., Mayo Clin. **12**:582-584 (Sept. 15) 1937.

69. Campbell, M. F.: Primary Malignant Tumors of the Urogenital Tract in Infants and Children, J. A. M. A. **109**:1606-1611 (Nov. 13) 1937.

From 2 to 11 per cent of malignant renal tumors occurring in children are hypernephromas. This type of tumor appears to be more frequent among girls. Hematuria is the dominant early symptom of hypernephroma in children, in contrast to the initial symptom of a mass in the loin, such as occurs with Wilms' tumor. Hematuria or a mass in the region of the kidney will direct attention to the urinary tract, but the diagnosis will rest chiefly on retrograde pyelographic studies.

Embryonal adenomyosarcoma (Wilms' tumor) is the most frequent neoplasm (one fifth of all tumors) of the urinary tract and abdomen occurring in young persons. Seventy-five per cent of Wilms tumors appear before the fifth year of life, and two thirds of them appear before the third year, which is the average age at which the tumors are first recognized. These growths have been observed in the fetus. After the seventh year, hypernephroma is more likely to occur than embryonal adenomyosarcoma.

A fifth of the patients who have Wilms' tumor have metastasis. The spread is characteristically through the blood stream, yet by lymphatic or direct extension the liver, the spleen, the spine, the intestine, the diaphragm and the lungs may be invaded. A tumor in the region of the kidney is the usual early sign of Wilms' tumor. Pain occurs in about 35 per cent of cases of Wilms' tumor. It results principally from capsular tension consequent to the enlarging parenchymal growth. Pain due to mass, weight or abdominal pressure is also frequent. Hematuria occurs late and is present in only about 15 per cent of cases. This is in contrast to its high incidence in cases of renal hypernephroma.

If there is doubt as to the correct diagnosis, a biopsy may be performed on material obtained by aspiration. The center of the tumor mass is determined by triangulation from a study of the urogram, and into this central region a needle (18 gage) attached to a 5 or 10 cc. syringe is plunged. Moderate suction is applied as the needle is introduced, and when it is at the desired depth the suction is increased sufficiently to draw out tissue for microscopic examination.

When only the usual surgical treatment, nephrectomy, is employed, the mortality is about 95 per cent. Only 5 of 55 patients lived longer than one year, a mortality of 91 per cent. The average life expectancy after nephrectomy alone is eight months; recurrences of the tumor are usually found after four months.

Preoperative radiation therapy apparently is a desirable addition in the treatment of this condition. In the employment of irradiation in treatment of the young, due caution must be observed, and vital organs, such as the liver, the spleen and the opposite kidney, must be protected. If the child withstands the treatment well, the total dose may be increased or the therapeutic period prolonged. After preoperative radiation the optimal time for operation appears to be from three to six

weeks. If treated with radiation the tumor becomes greatly reduced in size, but if nephrectomy is not performed within six weeks it recurs, and growths which follow irradiation are less radiosensitive than the original growth; they may even become radiation-fast, and the opportunity for cure may be lost. Beginning three or four weeks after removal of the tumor, a course of irradiation similar to the preoperative course, including irradiation of the regions of metastasis, is employed.

Tumors of the bladder are most unusual among children and are predominantly of mesodermal origin. The symptoms of tumor of the bladder are consequent to obstruction or to neoplastic ulceration. Thus, there are dysuria, frequent voiding and often burning and hematuria. When infection is present the urine is cloudy with pus.

Malignant growths of the penis and the urethra are almost unknown in the young. Urethral polyps are of frequent occurrence in children and merit consideration because they may produce obstruction and may be precancerous lesions.

Approximately 150 cases of tumor of the testicle among children have been reported. Of more than 300 patients treated by Dean for teratoma of the testis, only 2 were children, aged 3 and 4 years respectively. Examination of such growths shows them to be of congenital or embryonal origin; they have been observed at birth. The correct diagnosis of tumor of the testicle is suggested by palpation of a hard or enlarged nodular testis. In palpation of the enlarged testicle squeezing should be avoided, especially when the presence of tumor is suspected, lest malignant cells be forced into the circulation. The prognosis is always poor, and only by the employment of the method outlined in the following paragraph can one hope to reduce the high mortality which now generally exists.

Intensive preoperative and postoperative irradiation should be given in divided doses prior to orchidectomy. This treatment is applied to the local growth, isolaterally to the abdomen and to the lung or other regions in which metastasis has occurred. When the testicular tumor has diminished it may be removed with the region under local anesthesia.

Tumors of the prostate gland are extremely rare and among children are almost exclusively sarcomatous. The symptoms are those of urinary obstruction, often with hematuria and ultimately with chronic complete retention. The diagnosis is made by urologic examination, in which the rectal examination reveals a large mass filling the prostatic region and sometimes compressing the bowel.

Embryologically and endocrinologically the adrenal gland must be considered as intimately related to the urogenital tract. Benign adrenal tumors occasionally are seen post mortem in the young but are seldom encountered clinically except in rare instances of cortical or subcortical

growth, in which cases development of the genital tract and sexual precocity are striking manifestations. The important malignant adrenal tumor among children is neuroblastoma or neurocytoma, and, according to Campbell's observation, it occurs fully a third as often as do malignant renal tumors. Removal of the growth is the proper treatment, but in the case of adrenal tumor, too, intensive irradiation preoperatively and postoperatively, with divided doses, appears to offer the only hope for the reduction of the extremely high mortality.

UROLOGIC SURGERY

Priestley [70] stated that in 1936, 841 operations exclusive of transurethral procedures were performed on 758 patients for disease of the genitourinary system. There were 15 deaths in the entire group, or a gross mortality of 1.9 per cent.

Of the 245 patients who underwent operations on the kidney, 5 died, giving a mortality of approximately 2 per cent. Of patients who had operations on the kidney, 116 were operated on for nephrolithiasis. The next most frequent condition which required operation was hydronephrosis. Various changes have been instituted in the general management of nephrolithiasis in the past year. From the surgical point of view, a more thorough effort than ever before is being made to determine whether any obstruction to free renal drainage is present at the same time that stones are removed from the kidney. If obstruction is found, it is corrected when the stones are removed; therefore, plastic procedures now are combined with pelviolithotomy more frequently than in the past. Treatment of the infection which so frequently is associated with nephrolithiasis has undergone decided changes in the last year. It now includes the use of sulfanilamide and its derivatives and the continued use of mandelic acid and nonspecific injections of neoarsphenamine. These methods of treatment have supplanted largely the more cumbersome and difficult ketogenic diet.

Among the 47 patients operated on because of hydronephrosis, nephrectomy was performed on 31 and plastic procedures on the remaining 16. Of 29 patients on whom nephrectomy was performed for malignant tumors of the kidney, preoperative radiation was employed only in treating Wilms' tumor among children. Our experience with preoperative irradiation for adenocarcinoma or hypernephroma of the kidney among adults has not been as satisfactory as that reported by certain authors elsewhere. Among the 64 patients who underwent operation on the ureter there were 3 deaths. Ureterolithotomy was performed in 43 instances without a death. Two deaths occurred following transplantation of the ureter to the sigmoid flexure of the colon.

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70. Priestley, J. T.: Review of Urologic Surgery for 1936, Proc. Staff Meet., Mayo Clin. **12**:675-677 (Oct. 27) 1937.

Operation was performed on the bladder in 61 cases, with 6 deaths. Several of the patients who died had advanced carcinomatous lesions of the bladder, and the operation was considered purely palliative. In 40 of the 61 cases operation was performed for carcinoma of the bladder. The operation included excision, electrocoagulation, segmental resection and total cystectomy.

It is interesting to note that of the 752 patients treated for either benign or malignant prostatic hypertrophy in 1936, only 3 underwent perineal or suprapubic prostatectomy; the remainder were treated by transurethral prostatic resection, with gratifying results.

A new procedure for the treatment of hypospadias is being utilized. This entails implantation of a tubular skin graft to form the distal urethra. Although experience with this operation is as yet limited, good results have been reported by the originators of the procedure, and experience at the clinic up to the present time has given promise of gratifying results.

TRANSURETHRAL MANIPULATION

Thompson [71] reported on transurethral operations performed in 1936 at the Mayo Clinic. A total of 1,750 patients were subjected to 3,285 diagnostic or therapeutic procedures at the Colonial Hospital during 1936. An anesthetic was given in 1,521 instances. In 763, spinal anesthesia was employed; in 40, general anesthesia, and in 718, intravenous anesthesia. The agent used for intravenous anesthesia was practically without exception pentothal sodium. This drug continues to be satisfactory in urologic work and has been employed more extensively in general surgical practice in the past year.

In 35 cases radon seeds were implanted into tumors of the bladder. In some of these cases other surgical procedures, such as suprapubic segmental resection or some other attack through a suprapubic incision, had preceded the implantation of radon seeds by several months to a year. By this method, small recurrences of neoplasms of grade 3 or 4 occasionally can be controlled satisfactorily.

In 73 cases papillary tumors of the bladder were removed by transurethral methods. Fifty-five patients were subjected to 65 attempts to remove ureteral calculi, and in 54 cases the stone was removed. Litholapaxy was performed in 58 cases, in many of them as a procedure coincidental with transurethral prostatic resection. In 35 cases chronic prostatic abscesses were opened and minor operations were performed on the prostatic urethra to facilitate continued drainage and thus to obliterate the abscess cavities.

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71. Thompson, G. J.: Transurethral Surgery in 1936, Proc. Staff Meet., Mayo Clin. **12**:809-810 (Dec. 22) 1937.

In 749 cases, 835 resections of the prostate gland were done for benign or malignant enlargement causing obstruction to the flow of urine. It is interesting to note that only 3 per cent of the patients were less than 50 years of age, whereas 14.6 per cent were over 75. The average age for the entire group was 66.

The period of postoperative hospitalization was one week or less in 38.4 per cent of cases and more than three weeks in only 3.1 per cent.

The amount of tissue removed during the course of operation is interesting. In 211 cases it was 25 Gm. or more; in 1 instance 100 Gm. was removed at a single operation.

The mortality rate for the patients who underwent prostatic resection was a little higher than in preceding years. A total of 11 deaths occurred in the series of 749 cases, a mortality of nearly 1.5 per cent. There was no mortality with any of the other procedures.

CHYLURIA

Takahasi and Ikeda [72] were able to cure chyluria in a fair percentage of their cases (in all of which the condition was probably caused by filariasis) by simple injections of Ringer's solution into the renal pelvis. In 2 cases catheterization of the ureters alone was sufficient to produce this effect. Patients who were not cured were at least benefited by this treatment, as chyluria ceased for from five days to a year. The authors stated that hyperemia and stasis due to the injected solution or to catheterization tend to destroy the existing fistula between the lymphatic vessels and the renal pelvis. The condition is cured only when it is of recent occurrence; older processes are resistant to this form of treatment.

Wakefield and Thompson [73] reported a series of 5 cases of nonparasitic chyluria. Although more than 100 cases of nonparasitic chyluria have been reported in the literature, a critical review probably would exclude many of them, for only with extreme difficulty can the absence of Filaria bancrofti be proved. The diagnosis of nonparasitic chyluria can be made only after one is definitely sure that there has been no chance of exposure to filarial infestation. The voiding of chylous urine is the only symptom of the disorder. Coagulation of the urine before it is voided usually produces discomfort. The malnutrition of the patient can hardly be attributed to the loss of fat in the urine, for the equivalent of 400 calories is an unusually large output.

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72. Takahasi, S., and Ikeda, K.: Heilung der Chylurie durch Nierenbeckeneinspritzung von physiologischer Kochsalzlösung, Ztschr. f. Urol. **31**:729-736 (Nov.) 1937.

73. Wakefield, E. G., and Thompson, G. J.: Nonparasitic Chyluria, J. Urol. **38**:102-110 (July) 1937.

In the average case, each 100 cc. of urine contains between 500 and 1,000 mg. of fat.

In the 5 cases in Wakefield and Thompson's series, it was possible in only 1 case to visualize the perirenal lymphatics by pyelographic injection of opaque mediums. Subsequent pyelograms in this case showed normal conditions, and the excretion of chylous urine stopped abruptly after the injection of the opaque mediums. There seems to be no reason for discarding either the excretory or the mechanical hypothesis of chyluria, since there is not sufficient evidence to prove or to disprove either. Both hypotheses are theoretically possible. Pyelographic evidence is not sufficient to prove that lymphatic fistulas exist in every case.

URINARY ANTISEPTICS

Schulte [74] stated that Domagk deserves credit for the discovery of the value of the azo compounds containing the sulfonamide radical in the para position in the treatment of bacterial infections. Gelmo was the first to mention the drug which is now called sulfanilamide.

The international effort recently directed toward advances in bacterial chemotherapy leaves the clinician armed with sulfanilamide, a drug now in frequent use. However, a previous assumption that this is the pharmacologically effective portion of the molecule and is the chemotherapeutic bactericidal agent is now in question. Recently, investigations have demonstrated the streptococcicidal power of 4-4′-diaminodibenzenesulfone and 4-4′-dinitrobenzenesulfone. Independently and simultaneously Fourneau, Tréfouél, Nitti, Bovet and Tréfouél have proved that 4-4′-dinitrodibenzenesulfide and 4-4′-dinitrobenzenedisulfide have a similar property. Of interest is the fact that these drugs are more efficacious when given by mouth than when given by subcutaneous injection.

Gley also has worked with various compounds containing sulfur, and Girard, Ray and Richard, after much experimentation, concluded that sulfoxides, symmetric or asymmetric, containing groups OH, NH_2 or NO_2 in the para position, when administered by mouth, show an extremely high curative activity not only against streptococcic infections but also against experimental gonococcic infections.

Further experimental proof, therefore, must be awaited to decide what is the most pharmacologically effective drug for bacterial chemotherapy.

Helmholz and Osterberg [75] stated in a previous publication that the reaction of the urine has a definite effect on its bactericidal action after

74. Schulte, T. L.: History of the Development of Sulfanilamide (Para Amino Benzene Sulfonamide), Proc. Staff Meet., Mayo Clin. **13**:53-60 (Jan. 26) 1938.

75. Helmholz, H. F., and Osterberg, A. E.: The Effect of p_H of the Urine on the Concentration of Free and Conjugated Sulfanilamide Necessary for Bactericidal Action, Proc. Staff Meet., Mayo Clin. **12**:661-664 (Oct. 20) 1937.

sulfanilamide has been administered by mouth. They found that sulfanilamide is more effective in urine which has an alkaline reaction than in that which is acid. It was observed, too, that sulfanilamide in higher concentrations acts bactericidally in acid urine. The present study was undertaken for the purpose of determining the effectiveness of lower concentrations of sulfanilamide as a urinary antiseptic. Experiments were conducted by adding known quantities of sulfanilamide to samples of urine which contained certain types of bacteria. A comparison of the bactericidal action of free sulfanilamide added to the urine with that of the free and conjugated forms as excreted in the urine after administration of the drug by mouth also was made. It was found that the conjugated form seemed definitely more bactericidal than the free sulfanilamide. The following conclusions were reached:

1. In its free form, concentrations of only 25 to 40 mg. of sulfanilamide per hundred cubic centimeters of urine when added to an alkaline urine act bactericidally; concentrations as low as 25 to 30 mg. when excreted in alkaline urine act bactericidally.

2. The acetylated form of sulfanilamide does not act bactericidally in urine at a p_H of 7.8 at a concentration up to 200 mg. per hundred cubic centimeters.

UROGRAPHY

Stevens [76] stated that excretory urographic study furnishes sufficient data for exact diagnosis in a limited number of cases; in the others it must be supplemented by retrograde injection.

Better visualization of the renal cortex after excretory urographic examination is an important factor in the diagnosis of tumors of the kidney that do not involve or exert pressure on the renal pelvis or calices.

It is impossible to perforate a normal renal pelvis with an ordinary ureteral catheter. Extreme gentleness should be employed in the catheterization and injection of fluid into the renal pelvis when the patient is an infant or a young child. Injury to the kidney and also back flow are frequent during retrograde pyelographic examination.

Filling the kidney pelvis to the point of discomfort is sometimes a dangerous procedure. The principal danger accompanying extravasation into the parenchyma of the kidney and in the various types of back flow is the possible dissemination of infectious material.

Rupture extending through the capsule of the kidney is the most dangerous complication associated with retrograde pyelographic study.

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76. Stevens, W. E.: Roentgenologic Examination of the Kidney with Special Reference to Backflow and Injuries Associated with Retrograde Pyelography, Tr. Am. A. Genito-Urin. Surgeons **30**:169-182, 1937.

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